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REVIEW

Formation of a hard tissue barrier after pulp cappings in humans. A systematic review

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Abstract

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Aim To evaluate the evidence on the formation of a hard tissue barrier after pulp capping in humans.

Methodology A PubMed and CENTRAL literature search with specific indexing terms and a hand search were made. The authors assessed the level of evidence of each publication as high, moderate or low. Based on this, the evidence grade of the conclusions was rated as strong, moderately strong, limited or insufficient.

Results The initial search process resulted in a total of 171 publications. After reading the abstracts and hand searching the reference lists of the retrieved publications, 107 studies were retrieved in full-text and interpreted. After the interpretation, 21 studies remained and were included in the systematic review and given a level of evidence. No study had a high level of evidence, one study had moderate and 20 studies had a low level of evidence. There was heterogeneity between the studies; therefore, no meta-analysis was performed. The majority of studies on pulp capping using calcium hydroxide based materials reported formation of hard tissue bridging, studies on other pulp capping materials such as bonding agents presented inferior results. The evidence grade was insufficient.

Conclusions Insufficient evidence grade does not necessarily imply that there is no effect of a pulp capping procedure or that it should not be used. Rather, the insufficient evidence underpins the need for high-quality studies.

Keywords: calcium hydroxide, dental hard tissue formation, dental pulp capping, systematic review, treatment outcome.

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Introduction

Pulp capping is a treatment where a protective agent is applied to an exposed pulp to allow the pulp to recover and maintain its vitality and function. A pulp exposure is defined in the MeSH (Index Medicus: Medical Subject Headings) browser as 'the result of pathological changes in the hard tissue of a tooth caused by carious lesions, mechanical factors, or trauma, which render the pulp susceptible to bacterial invasion from the external environment' (http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=mesh). Ideally, the pulp exposure should be treated so that it will heal with new hard tissue forming a complete enclosure of the pulp. Hard tissue formation has been observed after different pulp capping procedures (Hellner 1930, Nyborg 1955). However, in long-term clinical follow-up studies of pulp capping performed with calcium hydroxide-based materials, failure-rates increase with increasing follow-up time. Therefore, the outcome has been considered uncertain (Hørsted *et al.* 1985, Barthel *et al.* 2000). One possible reason for the uncertain long-term prognosis is that no new

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hard tissue has been formed or that the newly formed hard tissue is not able to act as a functional barrier protecting the pulp against bacterial microleakage along the restoration margins.

When evaluating success or failure of the pulp capping procedure clinically, criteria such as sensitivity to electric pulp testing, radiological signs of apical pathology, pain and swelling have been used. These criteria may not reflect the hard tissue formation or the status of the pulp. To evaluate the status of the pulp and the formation of a hard tissue barrier after pulp capping with different procedures, the pulp and the hard tissue must be analysed with the aid of a microscope. The specimen must be serially sectioned since the hard tissue bridge may appear intact in some areas but defects may be unveiled in others (Cox *et al.* 1996).

The aim of this study was to evaluate the evidence on the formation of a hard tissue barrier after pulp capping by means of a systematic review. The systematic review will include studies of pulp capping in humans. The intended readers are oral biologists and dentists.

Materials and methods

To achieve a systematic approach, the literature search was conducted as described by Goodman (1993): (i) specify the problem; (ii) formulate a plan for the literature search; (iii) conduct a literature search and retrieve publications; and (iv) interpret and assess the evidence from the literature retrieved.

Specification of the problem

The following questions define the problem: can a pulp exposure heal, i.e. form a hard tissue barrier with a pulp tissue that is free of signs of inflammation after pulp capping? Under which circumstances does a hard tissue barrier form? What happens to the pulp and the newly formed hard tissue over time?

Systematic literature search

Pulp capping is described in the MeSH (Index Medicus: Medical Subject Headings) browser as 'the application of a protective agent to an exposed pulp in order to allow the pulp to recover and maintain its normal vitality and function' (http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=mesh). The pulp capping procedure may or may not include a partial pulp amputation. Procedures that included indirect pulp capping or stepwise excavation were not addressed.

Table 1 Data base search (PubMed) and number of publications retrieved

Indexing terms	Number of publications
# 1 ''Dental Pulp Capping'' [MeSH]	194
# 2 ''Case report'' [MeSH]	475 775
# 3 ''Dental Pulp Capping'' [MeSH] NOT ''Case report'' [MeSH]	171

Limits: Publication dates from 1 January 1966 to 1 January 2005 and indexed as 'only items with abstracts', 'English' and 'Human'. The search was performed on the 17 March 2005.

Publications were retrieved from PubMed using MeSH-terms as presented in Table 1. Only publications with abstracts and published in English were included. The search was limited to human material. Case reports were excluded. The PubMed search was combined with a search performed in The Cochrane Controlled Trials Register (CENTRAL) using the phrase 'pulp capping'.

To identify relevant publications, all abstracts obtained from the search in PubMed were read independently by the authors. Following publications were included:

1 Original scientific studies:
- human teeth with exposed pulps with or without caries treated with a pulp capping procedure;
- the hard tissue and the pulp should have been analysed with the aid of a microscope.

2 Reviews:
- the phrase 'pulp capping' should be written in the title or the abstract;
- the publication type should be indexed as Review.

When an abstract was considered by at least one author to be relevant, the publication was ordered in full text. For review articles, only the reference lists were used for further analysis.

The next step was to hand search all reference lists of publications that had been found to be relevant in the first step. Titles containing one of the phrases: pulp capping, pulp exposure, partial pulpotomy or vital pulp therapy were selected. Reviews and book chapters were excluded since the search in this step was focused on publications based on primary material. The literature search and retrieval of publications is presented in Fig. 1.

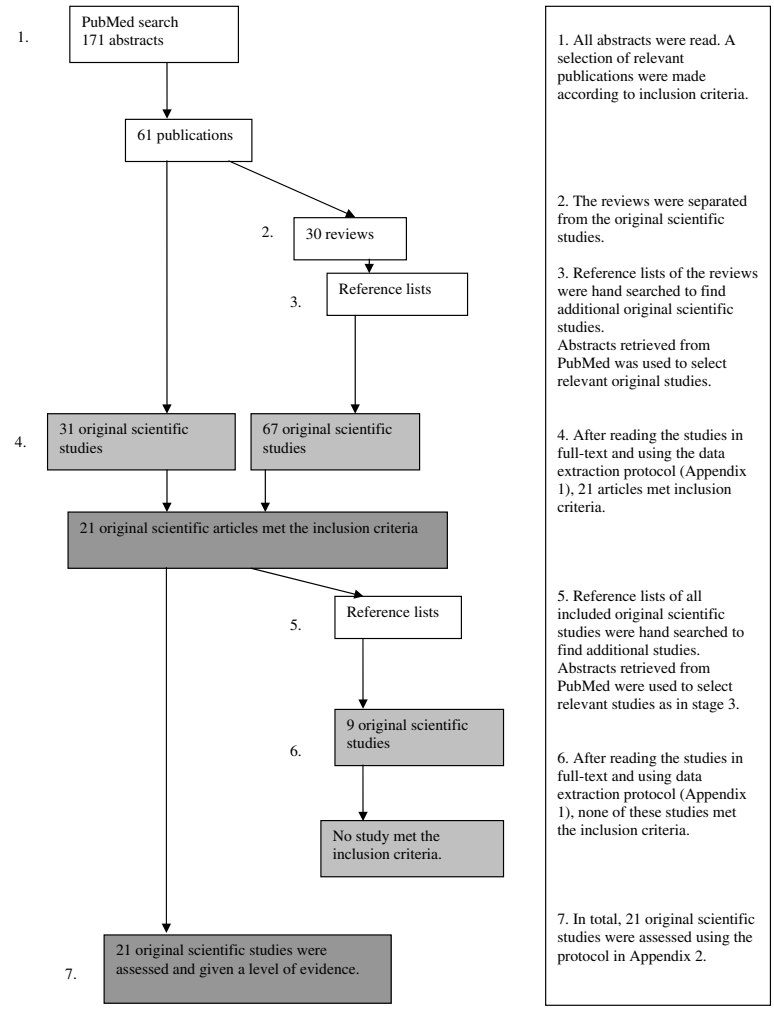

Figure 1. Literature search, data extraction and number of publications remaining in each stage (stages 1–7).

Table 2 Criteria used to define the study design when investigating effect of a health care intervention modified after Goodman (1993)

Randomized Controlled Trial (RCT): a true prospective experiment in which investigators randomly assign an eligible sample of patients to one or more treatment groups and a control group and follow patients' outcome.
Clinical Controlled Trial (CCT): a controlled study on human subjects intended to discover or verify the effects of an intervention.
Case–control study: a retrospective observational study in which investigators identify a group of patients with a specified outcome (cases) and a group of patients without the specified outcome (controls). Investigators then compare the histories of the cases and the controls to determine the extent to which each was exposed to the intervention of interest.
Series of cases: an uncontrolled (prospective or retrospective) observational study of an intervention and outcome in several single cases.

Interpretation and assessment of the publications included

Original scientific studies meeting the inclusion criteria were read, interpreted and assessed. The data extraction was performed independently by the authors according to the data extraction form presented in Appendix 1. The study design was defined according to the criteria presented in Table 2. The level of evidence, i.e. the quality and internal validity of each publication was assessed to be high, moderate or low independently by the authors according to criteria modified after 'Users' guides to the medical literature II. How to use an article about

Table 3 Levels of evidence and criteria for evidence synthesis

High level of evidence

The study was judged to have a high level of evidence if it fulfilled all of the criteria below:

- There was a sufficiently large sample of patients and teeth to detect a treatment effect, preferably calculated by a power analysis.
- The study was a true prospective experiment in which investigators randomly assigned the sample of patients and teeth to one or more intervention groups and a control group.
- The sample was described so that the pulp status was clear.
- The study personnel were blinded regarding the intervention.
- The procedure for performing the pulp capping was described in sufficient detail regarding size, type and site of exposure as well as materials used, to permit replication.
- There was a proper account of the patients and teeth that entered the trial and attributed to its conclusion.
- The analysis of the hard tissue formation and status of the pulp were adequate, i.e. the criteria were specified in the text or with a reference.
- The results were well documented and presented in terms of relevant data.

Moderate level of evidence

A study was judged to have a moderate level of evidence if any of the above criteria was not met. On the other hand, the study was judged not to have deficits that are described for studies with a low level of evidence.

Low level of evidence:

A study was judged to have a low level of evidence if it met any of the following criteria:

- There was not a sufficient large sample of patients and teeth.
- The sample and procedure was not described in sufficient detail to permit replication.
- There was no control group.
- The treatment and control group were not equal regarding preoperative status at the start of the trial.
- There was no clear statement of a randomization procedure of treatments.
- The withdrawals were large and not accounted for.
- The data was collected retrospectively.
- The sectioning and selection of sections to be stained were inadequately described.
- The analysis of the hard tissue formation and status of the pulp were not adequately described, i.e. the criteria were missing or not specified in the text or not referenced.

therapy or prevention' (Table 3) (Guyatt *et al.* 1993, 1994). The data extraction and the assessment of level of evidence were performed without blinding. The scientific evidence (evidence grade) of a conclusion was rated to be strong, moderately strong, limited, or insufficient, depending on the level of evidence of the publication (http://www.cebm.net/levels_of_evidence.asp).

Results

Systematic literature search

Using the MeSH term 'dental pulp capping' and excluding case reports as shown in Table 1, 171 abstracts were retrieved. After reading the abstracts a total of 61 abstracts (31 original scientific studies and 30 reviews) were considered relevant (Fig. 1). There was total agreement on 40 of the selected abstracts amongst the authors. After the hand search of the reference lists, a total of 107 original scientific studies were retrieved. Eighty-six publications did not meet the inclusion criteria, leaving 21 publications to be assessed and critically appraised. The number of original studies, that were retrieved in full text and excluded, and reasons for exclusion are listed in Table 4. The search in The Cochrane Controlled Trials Register did not identify any additional publications.

Table 4 Reasons for exclusion and number of excluded studies after retrieving them in full-text

Exclusion criteria	Number of excluded articles
Animal experiment	22
No histology	20
Full pulpotomy	13
No pulp exposure	7
Review	7
No light microscopic examination	5
No intervention	4
Impossible to assess data	3
No examination of the hard tissue	3
Case report	1
Non-English language	1
Total	86

Interpretation and assessment of the included studies

No publication was assessed to have a high level of evidence. One publication had a moderate level of evidence and 20 studies a low level of evidence. The fact that a large number of studies were assessed to have low levels of evidence was primarily because of fault in study design, sample size or the microscopic examination.

There was heterogeneity between the studies regarding the study design and pulp capping procedure (Table 5). Therefore, a meta-analysis was inappropriate to perform.

Several studies presented more than one observation period, reducing the sample size that ranged from 1 to 20 teeth per observation period. None of the studies reported a rationale for their sample size. The most common pulp capping procedure was direct pulp capping, two studies reported that a partial pulpotomy had been performed (Clarke 1971, Sübay *et al.* 1995). Most studies were performed in younger individuals and in healthy teeth, although four studies reported carious exposures and one study reported that the teeth had been intentionally contaminated during the pulp capping procedure (Cowan 1966, Clarke 1971, Stanley & Lundy 1972, Brännström *et al.* 1979, Fitzgerald & Heys 1991).

The sectioning and the selection of sections to be stained as well as the microscopic examination were accounted for in different ways. In six studies, there was no explicit description whether the specimens had been serially sectioned or not. One study stated that all histologic sections were analysed. However, there was no clear statement in this study that the teeth actually had been serially sectioned (do Nascimento *et al.* 2000). No studies used the same references when describing criteria for the analysis of the status of the pulp and the formation of hard tissue. Most studies used their own scales or specifications with no reference to previous studies.

Calcium hydroxide based materials

Eight studies remained for data extraction. They were assessed to have low level of evidence (Table 6). Different types of calcium hydroxide based materials; both mixtures with calcium hydroxide and commercial products such as Life (Kerr, Romulus, MI, USA) and Dycal (L.D. Caulk, Dentsply International Milford, DE, USA) were examined. Frequent hard tissue bridging was reported. The inflammation was judged to be none or slight, but there were reports of single teeth with necrosis (Fitzgerald & Heys 1991, Sübay *et al.* 1995). There were no reports of hard tissue bridging with shorter observation periods than 3 weeks.

Table 5 Data extraction regarding study design and procedure for performing the pulp exposure of the included studies ($n = 21$)

Study design	References
RCT	Brännström *et al.* (1979), Sübay *et al.* (1995), Demarco *et al.* (2001) and Hørsted-Bindslev *et al.* (2003)
CCT	Negm *et al.* (1980), Jerrell *et al.* (1984), Turner *et al.* (1987), Sübay & Asci (1993), Hebling *et al.* (1999), do Nascimento *et al.* (2000), Pereira *et al.* (2000), de Souza Costa *et al.* (2001) and Aeinehchi *et al.* (2003)
Case–control study	
Series of cases	Cowan (1966), Clarke (1971), Bhaskar *et al.* (1972), Stanley & Lundy (1972), Fitzgerald & Heys (1991), Kashiwada & Takagi (1991), Sari *et al.* (1999) and Cehreli *et al.* (2000)
Number of observational periods	
1	Stanley & Lundy (1972), Brännström *et al.* (1979), Fitzgerald & Heys (1991), Sübay *et al.* (1995), Sari *et al.* (1999) and Cehreli *et al.* (2000)
2	Negm *et al.* (1980), Jerrell *et al.* (1984), Turner *et al.* (1987), Pereira *et al.* (2000) and Demarco *et al.* (2001)
3	Kashiwada & Takagi (1991), Sübay & Asci (1993), Hebling *et al.* (1999), de Souza Costa *et al.* (2001) and Hørsted-Bindslev *et al.* (2003)
4	Cowan (1966), Bhaskar *et al.* (1972) and do Nascimento *et al.* (2000)
5	Aeinehchi *et al.* (2003)
6	Clarke (1971)
Placement of pulp exposure	
Buccal	Brännström *et al.* (1979), Jerrell *et al.* (1984), Turner *et al.* (1987), Sübay & Asci (1993), Hebling *et al.* (1999), Sari *et al.* (1999), Cehreli *et al.* (2000), do Nascimento *et al.* (2000) and de Souza Costa *et al.* (2001)
Occlusal	Cowan (1966), Kashiwada & Takagi (1991), Sübay *et al.* (1995), Pereira *et al.* (2000), Demarco *et al.* (2001), Aeinehchi *et al.* (2003) and Hørsted-Bindslev *et al.* (2003)
Unclear data	Clarke (1971), Bhaskar *et al.* (1972), Stanley & Lundy (1972), Negm *et al.* (1980) and Fitzgerald & Heys (1991)

Table 6 Data from studies on pulp capping in humans using calcium hydroxide based materials. Unclear data reported with '?'

Author name and year	Method [*study design and observation time(s)*]	Material [*test (T), number of teeth; control (C), number of teeth; number of subjects*]	Reported results [*test (T), control (C)*]	Level of evidence and comments
Stanley & Lundy (1972)	Series of cases 1–330 days	T: Dycal, $n = 35$ C: – Subjects, $n = 10$	Various stages of hard tissue formation in 19 of 35 teeth. Pulp condition: optimal in 27 teeth, fair in five and poor in three	Low No control, microscopic examination not adequately described
Brännström *et al.* (1979)	RCT 7–10 weeks	T: Calcium hydroxide + calcium monofluorphosphote in Ringer's solution after cleaning with various forms of Tublicid, $n = 15$ C: Calacept after cleaning with various forms of Tublicid, $n = 15$ Subjects, $n = 15$	No difference between T and C All teeth had a barrier, or were forming a barrier All teeth free of inflammation except for one	Low No data on number of teeth with complete barrier, microscopic examination not adequately described
Negm *et al.* (1980)	CCT Two observation intervals between 7–12 and 45–60 days	T1: 25% calcium hydroxide and 75% zinc oxide with 42% aqueous solution of polyacrylic acid, $n = 20$ T2: 50% calcium hydroxide and 75% zinc oxide as above, $n = 18$ C: Dycal, $n = 19$ Subjects, $n = ?$	At 60 days: T1: dentine bridging in nine of 10 T2: dentine bridging in eight of eight C: Dentine bridging in eight of 10 No inflammation	Low No randomization, sample size too small to detect difference in treatment effect. Number of subjects not described
Jerrell *et al.* (1984)	CCT Two observation intervals: 7 and 63 days	T: Life, $n = 22$ C: Dycal, $n = 22$ Subjects, $n = 15$	No difference between T and C. Matrix barrier in 18 of 18 after 63 days, and inflammation judged successful	Low No randomization, sample size too small to detect difference in treatment effect
Turner *et al.* (1987)	CCT Two observational intervals: 7 and 63 days	T1: Nu-cap, $n = 24$ T2: Dycal, $n = 22$ T3: Life, $n = 21$ C: Calcium hydroxide mixed with saline, $n = 24$ Subjects, $n = 34$	At 63 days: T1: seven of 14 complete dentine bridge T2: six of 18 complete dentine bridge T3: four of 18 complete dentine bridge C: 12 of 14 complete dentine bridge Test materials less inflammation than in control	Low No randomization, material from two separate studies. Microscopic examination not adequately described
Fitzgerald & Heys (1991)	Series of cases 6 months	T1: Life, $n = 8$ T2: Dycal, $n = 8$ Intact teeth, $n = 7$ Subjects, $n = ?$	No difference between T1 and T2. Formation of dentine bridges. None to slight inflammation, two teeth with necrosis	Low Sample size too small to detect difference in treatment effect

Table 6 (Continued.)

Author name and year	Method [*study design and observation time(s)*]	Material [*test (T), number of teeth; control (C), number of teeth; number of subjects*]	Reported results [*test (T), control (C)*]	Level of evidence and comments
Sübay *et al.* (1995)	RCT 4 months	T: Dycal, $n = 10$ C: Pulpdent Multi-Cal, $n = 10$ Subjects, $n = 7$	T: Dentine bridge formation in all teeth and no inflammation C: Dentine bridge formation at some distance from the test material in six of 10, and various stages of inflammation, one tooth showed necrosis	Low Sample size too small to detect difference in treatment effect
Sari *et al.* (1999)	Series of cases 90 days	T: Calcium hydroxide mixed with saline, $n = 20$ C: – Subjects, $n = 14$	Dentine bridge in all teeth and some inflammation	Low No control. No serially sectioning

Bonding materials

Seven studies, one with moderate and six with low levels of evidence, remained (Table 7). There were reports of single teeth where a hard tissue bridge had been formed (Bhaskar *et al.* 1972, Kashiwada & Takagi 1991, Cehreli *et al.* 2000, Demarco *et al.* 2001). In a control group where calcium hydroxide based material was used, a higher frequency of hard tissue bridge formation and a lower degree and frequency of inflammation was observed compared with the test group using a bonding material (Hebling *et al.* 1999, Pereira *et al.* 2000, Demarco *et al.* 2001, de Souza Costa *et al.* 2001, Hørsted-Bindslev *et al.* 2003).

Other materials

Other materials used included Ledermix (Lederle Pharmaceuticals, Wolfrantshausen, Germany), Vitrebond (3M Dental Products Division, St Paul, MN, USA), synthetic hydroxyapatite, isobutyl cyanoacrylate and mineral trioxide aggregate (MTA) (ProRoot, Dentsply, Tulsa, OK, USA). All six studies were assessed to have low levels of evidence (Table 8). One study analysing MTA as a pulp capping material reported hard tissue bridging (Aeinehchi *et al.* 2003).

Concluding evidence grade

The heterogeneity amongst the assessed studies was substantial. One of 21 studies had a moderate level of evidence; consequently, the total evidence grade was insufficient.

Discussion

Methodological considerations

The assessment of the quality and internal validity of each study undertaken here, assessed what was reported in the publication. Thus, the randomized controlled trial (RCT) classification was used exclusively for those studies where it was clearly stated.

Choosing to study the newly formed hard tissue and the status of the pulp with the aid of a microscope may be considered a surrogate endpoint. What really should be the focus is how well the newly formed hard tissue can act as a barrier withstanding a late exposure to the oral microflora, or even better; how long the pulp capped tooth may stay functional in the mouth in a healthy state to prevent spreading of infection.

Table 7 Data from studies on pulp capping in humans using bonding materials. Unclear data reported with '?'

Author name and year	Method (*study design and observation time*)	Material [*test (T), number of teeth; control (C), number of teeth; number of subjects*]	Reported results [*test (T) and control (C)*]	Level of evidence and comments
Kashiwada & Takagi (1991)	Series of cases Three observation intervals: 1, 6 and 12 months	T: Clearfil Photo Bond, $n = 6$ C: – Subjects, $n = 5$	A thin bridge of dentine at 12 months. No inflammation	Low No control, microscopic examination not adequately described
Hebling *et al.* (1999)	CCT Three observation intervals: 7, 30 and 60 days	T: All Bond 2 dentine adhesive system, $n = 18$ C: Calcium hydroxide mixed with saline covered by Dycal, $n = 12$ Intact teeth, $n = 2$ Subjects, $n = ?$	T: No dentine bridge formation and slight to severe inflammation C: Dentine bridge and no inflammation at 60 days in 4 of 4	Low No randomization
Cehreli *et al.* (2000)	Series of cases 60 days	T1: Scotchbond Multi Purpose Plus, $n = 7$ T2: Prime & Bond 2.1, $n = 7$ T3: Syntac Single Component, $n = 7$ C: – Subjects $n = 7$	Attempted dentine bridge formation in two of 21 Slight inflammation to necrosis	Low No control
Pereira *et al.* (2000)	CCT Two observation intervals: 9–12 and 53–204 days	T: Scotchbond Multi-Purpose Plus, $n = 27$ C: Calcium hydroxide covered by Dycal, $n = 24$ Subjects, $n = ?$	T: No dentine bridge formation, various stages of no inflammation to necrosis C: Dentine bridge formation in five of 10 at 53–90 days. No or minimal inflammation	Low No randomization
Demarco *et al.* (2001)	RCT Two observation intervals: 30 and 90 days	T1: Scotchbond Multi-Purpose Plus, $n = 8$ T2: Clearfil Liner Bond 2, $n = 8$ C: Calcium hydroxide powder covered with Hidro C, $n = 4$ Subjects, $n = 6$	T1: No dentine bridge formation, mild to severe inflammation T2: three of eight dentine bridge formation, no or mild inflammation C: Dentine bridge formation without inflammation in 4 of 4	Low Sample size too small to detect difference in treatment effect
de Souza Costa *et al.* (2001)	CCT Three observation intervals: 5, 30 and 120–300 days	T: Clearfil Liner Bond 2, $n = 17$ C: Calcium hydroxide mixed with saline and covered by Dycal, $n = 15$ Intact teeth, $n = 3$	T: Some hard tissue formation but no dentine bridge formation. Mild to moderate inflammatory response. C: Dentine bridge formation, no inflammation	Low No randomization, sample size too small to detect a difference in the treatment effect
Hørsted-Bindslev *et al.* (2003)	RCT Three observation intervals: 7, 10–15 and 56–71 days	T: Single Bond, $n = 17$ C: Dycal, $n = 17$ Subjects, $n = 16$	T: No complete hard tissue formation, two of 10 incomplete hard tissue formation. Slight to moderate inflammatory reaction C: Five of 11 complete and three of 11 incomplete hard tissue formation. Few inflammatory cells	Moderate The results were incomplete regarding documentation and presentation in terms of relevant data. Two observational intervals are accounted for

Table 8 Data from studies on pulp capping in humans using other materials than calcium hydroxide based and bonding agents. Unclear data reported with '?'

Author name and year	Method (*study design and observation time*)	Material [*test (T), number of teeth; control (C), number of teeth; number of subjects*]	Reported results [*test (T) and control (C)*]	Level of evidence and comments
Cowan (1966)	Series of cases One observation interval 4–8 weeks in the noncarious group and four observation intervals between 14 and 43 days in the carious group	T: Ledermix in two different vehicles Noncarious, $n = 29/2$? Carious, $n = 7$? C: Zinc oxide eugenol noncarious, $n = 29/2$? Carious, $n = 2$? Subjects, $n = ?$	T: No hard tissue bridge in the two groups. Inflammation to necrosis C: No hard tissue bridge. Inflammation, often severe to necrosis	Low Imprecise data on number of teeth and subjects, microscopic exam ination not adequately described
Clarke (1971)	Series of cases Six observation intervals between 24 h, 1, 2, 4, 8, 20 and 48 weeks	T: Ledermix incorporated in fibres of cotton wool, $n = 21$ C: After surgery the teeth were extracted immediately with no intervention, $n = 4$ Subjects, $n = ?$	No hard tissue bridge was formed Inflammation, often severe	Low No control with an intervention, microscopic examination not adequately described
Bhaskar *et al.* (1972)	Series of cases Four observation intervals: 0–2, 3–4, 5–13 and 22 weeks	T: Isobutyl cyanoacrylate, $n = 19$ C: – Subjects, $n = ?$	Four of 15 complete dentine formation Five of 19 microabscesses Four of 19 subadjacent necrosis	Low No control, microscopic examination not adequately described
Sübay & Asci (1993)	CCT Three observation intervals: 2, 30 and 60 days	T: Particles of synthetic hydroxyapatite, $n = 22$ C: Dycal, $n = 22$ Subjects, $n = 20$	T: No hard tissue bridging, inflammation C: Hard tissue bridge in nine of 10 at 30 days and in eight of nine at 60 days and minimal inflammation. One tooth showed partial necrosis	Low No randomization
do Nascimento *et al.* (2000)	CCT Four observation intervals: 5, 30, 120 and 300 days	T1: Vitrebond, $n = 16$ T2: Calcium hydroxide mixed with saline covered by Dycal, $n = 15$ C: Intact teeth, $n = 3$ Subjects, $n = ?$	T1: No dentine bridging and slight inflammation T2: Dentine bridging in five of five and less inflammation than T1 at 120–300 days	Low No randomization T1 and T2 mixed up in table presenting results Not obvious whether the teeth had caries or were inflamed prior to the intervention
Aeinehchi *et al.* (2003)	CCT Five observation intervals: 1 week, 2, 3, 4 and 6 months	T: Mineral trioxide aggregate (MTA), $n = 8$ C: Dycal, $n = 6$ Subjects, $n = 11$	T: Dentinal bridge in seven of eight, no or mild inflammation C: Dentinal bridge in four of six, mild to severe inflammation	Low Large drop-out of patients

When presenting the results, it is important to describe criteria for the way all the serial sections have been analysed. There were different criteria to classify the histological findings of the newly formed hard tissue and the status of the pulp. Some were purely descriptive. In some studies, it was difficult to relate the results regarding the formation of hard tissue to the status of the pulp. As the criteria were diverse, it was difficult to compare the results between the studies.

Results

It seems that it is possible for the pulp to heal with hard tissue after a pulp capping procedure. The studies using calcium hydroxide-based material presented a large number of teeth with hard tissue bridges. These results were in accordance with those of animal studies (Pitt Ford 1985, Cox *et al.* 1996). Pulp capping using bonding materials reported a few hard tissue bridges and a more pronounced inflammation compared with the calcium hydroxide-based materials. The reason for this may be that the bonding materials are toxic to the pulp tissue or that the material does not work as a barrier against late infection from the oral flora. The results from this systematic review regarding bonding materials were in contrast to the reported results from pulp capping procedures in studies performed in animals (Olmez *et al.* 1998, Kitasako *et al.* 1999).

One of the aims of the present study was to analyse under what circumstances a hard tissue barrier forms. However, this was not possible to analyse. Information concerning the way in which factors such as the patient's age, type and site of exposure or the pre-operative status of the tooth affect the ability to form a hard tissue bridge after pulp capping was not found.

No studies elucidating 'What happens to the pulp and the newly formed hard tissue over time?' were found. Although there were studies with observation periods of up to 300 days, this is still too short to evaluate the long-term outcome. There were different observational periods in the studies. Periods shorter than 3 weeks seem to be associated with no reports of hard tissue bridges.

In most studies, the pulp exposure was performed in young healthy teeth. Pulp exposures in noninflamed teeth may be found in conjunction with trauma, a condition which occurs relatively seldom. Most often the pulp is exposed due to caries, and the pulp is subsequently inflamed with various grades of severity. To achieve an external validity in future pulp capping studies, the selection of subjects and teeth should be made in such a way that they reflect the clinical situation when most pulp exposures are made, i.e. in inflamed pulps due to caries in subjects of all ages. Different results can probably be expected when pulp capping is performed in teeth with inflamed pulps.

Concluding evidence grade

Based on this systematic review, the evidence grade of the conclusion was insufficient. The fact that the evidence grade was insufficient does not necessarily imply that there is no effect of pulp capping or that it should not be used. The results point to the need for high-quality studies in future research. To improve the evidence, the study design ought to be RCTs with a sample size that is large enough to detect a difference in the treatment effect. The sample size should preferably be calculated before starting a trial and be based on the anticipated difference in effect that is considered clinically significant. To be able to detect a small expected difference between two pulp capping materials, a large sample size is required in contrast to a large expected difference in treatment effect that can be proven in a smaller sample size. None of the included articles reported a rationale for their sample size.

It is essential that a control group is used, preferable a calcium hydroxide based material, as it seems likely that such materials have the most consistent ability to form a hard tissue barrier. To be able to use the data from pulp capping studies, it is important that studies are conducted in settings that reflect the situation where most pulp exposures are being made, i.e. in inflamed pulps due to caries.

Conclusions

No publication was assessed to have a high level of evidence. One publication had a moderate level of evidence and 20 studies had a low level of evidence. The insufficient evidence does not necessarily imply that there is no effect of a pulp capping procedure or that it should not be used. Since the current knowledge is limited, there is a need for more high-quality studies.

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Appendix 1

Protocol 1. Data extraction Pulp capping in humans

First author: ……Title: ……

Journal: ……Year: …… Volume: ……Pages: ……...

Was there a clear research question / hypothesis / aim of the study to address?

☐ Yes ☐ Cannot be decided ☐ No

Study design

☐ RCT (Randomized Controlled Trial) ☐ CCT (Clinical Controlled Trial)

☐ Case-control ☐ Series of consecutive cases

☐ Other: …….

Description of the subjects

Age Mean:…… Range:……

Number of patients:……. Number of teeth: ……

☐ Permanent teeth ☐ Primary teeth Type of teeth: ……..…… ☐ Can't tell

☐ Mature root ☐ Immature root ☐ Can't tell

☐ Noncarious/intact teeth ☐ Caries/inflammation in the pulp ☐ Can't tell

☐ Other:…… Exclusion criteria:……

How was the pulp exposed? ☐ Direct pulp capping ☐ Partial pulpotomy

Where was the pulp exposed? ☐ Occlusal, class I ☐ Buccal, class V

Size of the exposure:…… ☐ Can't tell

Test material (pulp capping material)

☐ Calcium hydroxide, powder ☐ Calcium hydroxide, powder mixed with water/saline

☐ Calcium hydroxide, brand name:……. ☐ Other: ……

Number of patients treated with test material: …… ☐ Can't tell

Number of teeth treated with test material: ……. ☐ Can't tell

Type of filling: …… ☐ Can't tell

Control material

Was there a control? ☐ Yes ☐ No

If yes, what material was used?

☐ Calcium hydroxide, powder ☐ Calcium hydroxide, powder mixed with water/saline

☐ Calcium hydroxide, brand name: …… ☐ Other:…….

Number of patients treated with control material: …… ☐ Can't tell

Number of teeth treated with control material: …… ☐ Can't tell

Type of filling: ……. ☐ Can't tell

Were all patients or teeth that entered the trial properly accounted for and attributed at its conclusion? ☐ Yes ☐ No ☐ Can't tell
Comments: ……...

How long was the observation period(s): ……

How were the teeth prepared for the microscopic examination?
☐ Serial sectioning. Thickness of the sections: ……..☐ Other: …… ☐ Can't tell
Number of sections analysed: …… ☐ Can't tell
Staining: ☐ Haematoxylin and eosin ☐ Other: …… ☐ Can't tell

What kind of microscopic technique was used in order to assess the treatment results?
☐ Light microscope ☐ Scanning microscope ☐ Transmission microscope
☐ Other: …… ☐ Can't tell
Analysis of hard tissue and status of pulp
How was the hard tissue formation assessed? ☐ No record ☐ Descriptive
☐ Specified according to a reference or in the article:…….
How was the status of the pulp assessed? ☐ No record ☐ Descriptive
☐ Specified according to a reference or in the article: ……

Relevance to the project: ☐ Yes ☐ No. Why? ☐ Case Report ☐ Review
☐ Non-English literature ☐ No pulp exposure ☐ Full pulpotomy
☐ Animal experiment ☐ No histology

What were the results regarding the hard tissue formation and the status of the pulp?
……...
Did one course of action lead to important gains regarding new hard tissue formation?
☐ Not reported ☐ No ☐ Yes If yes, specify: ……...
Did one course of action lead to important gains regarding the status of the pulp?
☐ Not reported ☐ No ☐ Yes If yes, specify:……

Interpretation made by: Date:

Appendix 2

Protocol 2. Level of evidence pulp capping in humans
First author: ……
Title: ……
Journal: ……Year: ……. Volume: …… Pages: ……

Are the results of the study valid?

Was the sample described in sufficient detail concerning:

- Number of patients and teeth Yes No
- Status of tooth (caries, inflammation etc) prior to the intervention Yes No
- Type of teeth Yes No

Did the sample size appear sufficiently large to detect a treatment effect? Yes No

Was the procedure for performing the pulp capping described in sufficient detail to permit replication regarding:

- Type and size of exposure Yes No
- Site of exposure Yes No
- Materials used Yes No

Was there a control group? Yes No
If answer is 'yes':
Was the assignment of patients/teeth to treatments randomized? Yes No
Were the groups similar at the start of the trial? Yes No
Aside from the experimental intervention, were the groups treated equally? Yes No

Was the study personnel blinded? Yes No

Were all objects that entered the trial properly accounted for and attributed at its conclusion? Yes No

Was there an adequate description of the microscopic examination? Yes No
Was the analysis of treatment results adequate, *i.e.* specified in the text or with a reference, regarding:

- Hard tissue formation Yes No
- Status of the pulp Yes No

What are the results?

Were the results well documented to present important gains for the healing process regarding:

- Hard tissue formation Yes No
- Status of the pulp Yes No

Was the estimate of the treatment effect precise? Yes No

Level of evidence ☐ High ☐ Moderate ☐ Low
Reasons: ……