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Comparative Effectiveness Research for Direct Pulp Capping Materials

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Comparative Effectiveness Research for Direct Pulp Capping Materials

A thesis submitted in partial satisfaction of the requirements
for the degree Master of Science in Oral Biology

by

Khaled Alghulikah

2016
ABSTRACT OF THE THESIS

Comparative Effectiveness Research for Direct Pulp Capping Materials

by

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Master of Science in Oral Biology

University of California, Los Angeles, 2016

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Introduction:
Dental caries is one of the most common chronic diseases in the world. In daily dental practice, dentists are treating many cases where the destruction from caries involves enamel and dentin and reaches the pulp. One of the main objectives of a restorative dental procedure is the protection of the pulp to maintain its vitality, and pulp capping has been shown to be very successful in this regard for cases of reversible pulpitis. When the carious lesion is in close proximity to the pulp but the pulp tissue has not been exposed, indirect pulp capping is performed using any of several liner or base materials prior to placing the final restoration. On the other hand, if there is a direct exposure to the pulp, treatment with direct pulp capping requires careful and specific selection of the pulp capping material.

In the past decade, there has been a debate on the best available material to be used in direct pulp capping. Calcium hydroxide was considered the gold standard material used for direct pulp
capping for decades prior to the introduction of Mineral Trioxide Aggregate (MTA). Many studies have been conducted to study the effectiveness of these materials when used in direct pulp capping. The purpose of this study is to identify the best available evidence on direct pulp capping material and determine if MTA is more effective than calcium hydroxide.

**Methods:**
The research strategy included search engines and hand searching to obtain randomized clinical trials and systematic reviews relevant to the research question. The search engines used were PubMed, ADA Evidence Base Database, Cochrane library and Web of science. Two readers were involved in validating the quality of the evidence and strength of recommendation in randomized clinical trials using Ex-GRADE and the revised risk of bias instruments. Acceptable sampling will be completed prior to performing Meta-analysis. Similarly, (R-AMSTAR) instrument was used to quantify the quality of systematic reviews.

**Results:**
The bibliome consists of seven clinical trials, five observational studies and four systematic reviews. The acceptable sampling analysis produced three systematic reviews, two clinical trials and four observational studies. Qualitative assessment of the accepted studies confirmed that MTA is more effective and shows better clinical outcomes in direct pulp capping procedure when compared to calcium hydroxide.

**Conclusion:**
This review confirms that direct pulp capping is an effective conservative approach to maintain the vitality of dental pulp tissue. Qualitative consensus of the research confirmed that MTA showed a higher success rate, reduced pulpal inflammation, and had a more reparative dentin formation
when used for direct pulp capping. Calcium hydroxide showed more failures compared to MTA, and the superiority of MTA was confirmed in short and long periods of follow up.

Key words: Pulp capping, dental Pulp Capping, direct pulp capping, evidence-based dentistry, Calcium Hydroxide, Dycal, Ca(OH)2, Mineral Trioxide Aggregate, MTA, GMTA, WMTA and ProRoot MTA.
The thesis of Khaled Alghulikah is approved.

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University of California, Los Angeles

2016
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Chapter 1

Introduction

1. Background
Success in the daily dental practice demands understanding of the anatomic and biologic structure of the tooth (Schwartz, Summitt, & Robbins, 1996). Restorative dentistry is a conservative approach to treating structural defects in teeth structure and maintaining their functionality. Destruction of tooth structure can be classified into two main categories, carious and non-carious lesions. Caries is defined as “an infectious microbiologic disease of the teeth that results in localized dissolution and destruction of the calcified tissues.” It is one of the most prevalent chronic diseases throughout the world (Roberson, Heymann, Swift, & Sturdevant, 2006). Non-caries tooth structure loss occur as the result of abrasion, erosion, attrition, abfraction and fractures.

Pulpal protection is one of the main objectives of restorative dental treatment when a mechanical alteration of the defective tooth structure is performed. Tooth preparation for restoration placement requires removing all the defective structure as well as providing pulpal protection against irritants (Roberson et al., 2006). In fact, mechanical, chemical or thermal irritants might affect the status of the pulp tissue and lead to inflammation or necrosis. Pulpal protection during the tooth preparation procedure includes: adequate air-water cooling, light pressure, preservation of the sound tooth structure as well as applying cavity liners or sealers to prevent thermal irritation and bacterial invasion (Schwartz et al., 1996).
Bacterial invasion of the pulp is the main cause of pulpal pain and discomfort in cases of pulpal inflammation, also known as pulpitis. However, a painful pulpal reaction might be seen in some cases with no direct exposure of the pulp tissue to bacteria. The thermal sensitivity and pain in these cases are explained by the hydrodynamic theory, which is the most universally accepted theory for the mechanism of tooth pain (Schwartz et al., 1996). The theory ascribes the pain in the absence of bacterial invasion to the movement of fluid in the dentinal tubules caused by osmotic or physical stimuli and resultant transmission of the stimuli to odontoblast cells and nerve fibers in the pulp. In fact, many studies have shown that there is an association between deep restorations and increased sensitivity due to the exposed dentinal tubules and increased permeability. Accordingly, air-water cooling during tooth preparation is important to avoid increasing the heat and damaging the odontoblast cells (Roberson et al., 2006).

Inflammation of the pulp tissue may be diagnosed as reversible or irreversible pulpitis. The American Association of Endodontics defines reversible pulpitis as “A clinical diagnosis based on subjective and objective findings indicating that the inflammation should resolve and the pulp return to normal”("AAE Consensus Conference Recommended Diagnostic Terminology,"). In contrast, if the pulp is diagnosed as irreversible pulpitis that indicates that the tissue is incapable of healing ("AAE Consensus Conference Recommended Diagnostic Terminology,"). In cases of reversible pulpitis, the application of cavity liners is essential for both healing of the pulp and maintaining healthy pulpal status. Cavity liners when applied with minimal thickness can provide antibacterial action and therapeutic benefits to the pulp (Schwartz et al., 1996).

The procedure of applying cavity liners or sealers during the tooth preparation is known as pulp capping. The definition of pulp capping is “Endodontic treatment designed to maintain the vitality of the endodontium” (Schwartz et al., 1996). There are two types of pulp capping.
Indirect pulp capping involves placing a cavity liner or sealer on remaining dentin or residual caries. Placement a liner is placed over an exposed pulp is defined as direct pulp capping (Hilton, 2009). The placement of a pulp capping material protects the pulp tissue and enhances reparative dentin formation (Schwartz et al., 1996). The importance of studying the pulp capping materials is based on the fact that many studies have shown that pulpal inflammation may not be associated with the presence of bacteria. Therefore, certain pulp capping materials have the ability to provoke inflammatory response (Hilton, 2009).

Prior to the placement of a pulp capping material, the following requirements for performing direct or indirect pulp capping must be confirmed:

1. Vital pulp tissue
2. No lingering pain to thermal stimuli
3. No radiographic of periapical lesion
4. Placement of permanent restoration to exclude bacteria (Schwartz et al., 1996).

The placement of a sealed permanent restoration has shown in several studies to be the most important factor for success in pulp capping procedures. Indeed, T.J. Hilton concluded in a systematic review published in 2009 that “the key to pulp survival after capping is a well-sealed restoration” (Hilton, 2009).

**Indirect Pulp Capping**

In deep caries lesions, it is suggested to avoid exposing the pulp if no signs or symptoms of irreversible pulpitis is present (Hilton, 2009). Therefore, in these cases performing indirect pulp capping is more favorable than direct pulp capping. During the tooth preparation procedure, demineralized dentin is excavated from the peripheries, and a small amount is left over the pulp. Prior to the placement of the permanent restoration, a liner or sealant is placed over the remaining
caries to seal the bacteria and bacterial by-products (Schwartz et al., 1996). Recommendations in the past suggested placement of a temporary restoration over the cavity liner and evaluate the case after eight weeks (Roberson et al., 2006). However, recent and current studies recommend performing pulp capping and placing the final restoration during the same visit (Hilton, 2009).

Incomplete caries removal has been suggested by many studies to show equal outcomes when compared to complete removal of caries (Hilton, 2009). Clinical trials have shown that there is no harm in leaving infected dentin over the pulp (Thompson, Craig, Curro, Green, & Ship, 2008). Moreover, several studies concluded that caries control does not require removal of all carious dentin (Thompson et al., 2008). A study conducted by Mertz-Fairhurst EJ in 1998, showed that a sealed restoration over the caries arrests its progression by eliminating the availability of a fermentable substrate to the bacteria. The cases were evaluated over a period of ten years (Mertz-Fairhurst, Curtis, Ergle, Rueggeberg, & Adair, 1998).

Traditionally, several materials have been suggested for use as a liner for indirect pulp capping procedures. Calcium hydroxide was the most commonly used material since it showed an ability to stimulate reparative dentin bridge formation. The placement of a sealed base of resin modified glass ionomer may improve the clinical result of indirect pulp capping (Hilton, 2009).

**Direct Pulp Capping**

Direct pulp capping is defined as a procedure of placing a medicament or restorative material over the exposed pulp to maintain the vitality of the pulpal tissue (Hilton, 2009; Mente, Geletneky, Ohle, Koch, Ding, et al., 2010). Successful direct pulp capping prevents the need for more complex or invasive treatment options such as root canal therapy or extraction (Li, Cao, Fan, & Xu, 2015). Direct exposure of the pulp can happen due to mechanical mishaps and trauma, in
addition to excavating deep caries (Hilton, 2009). There are several factors that can increase the success of direct pulp capping, such as the following:

1. Asymptomatic tooth with no history of spontaneous or lingering pain.
2. Less than 0.5mm pulp exposure.
3. Controlled pulpal bleeding after exposure.
4. Proper isolation of the tooth during the procedure.
5. Minimal blood contamination of adjacent dentin (Roberson et al., 2006).

Several materials have been used for direct pulp capping over the years. Some of these materials have shown to promote pulpal healing, while other liners are no longer recommended to be used based on clinical studies that indicated poor outcomes (Hilton, 2009). The most reviewed direct pulp capping materials in the literature are: zinc oxide eugenol, glass ionomer, bonding agents, calcium hydroxide and mineral tri oxide aggregate (Hilton, 2009; Roberson et al., 2006).

**Zinc Oxide Eugenol**

Zink oxide eugenol is frequently used in daily dental practice as a cavity base or temporary restorative material (Hilton, 2009). Additionally, it was suggested to use zinc oxide eugenol as a pulp capping material to produce a palliative and sedative response of the pulp tissue (Roberson et al., 2006). However, a study conducted on the use of zinc oxide eugenol for direct pulp capping showed poor clinical results and chronic inflammation of the pulp (Hilton, 2009).

**Glass Ionomer**

Glass ionomer and resin modified glass ionomer have been suggested for use as a base under gold, amalgam or ceramic restorations due to its ability to seal to the dentin and prevent bacterial invasion (Hilton, 2009; Roberson et al., 2006). Glass ionomer has also been recommended as a
sealer under composite restorations to eliminate micro-leakage (Schwartz et al., 1996). In direct pulp capping, both materials are considered cytotoxic when used in direct contact with the pulp tissue. A study performed on resin modified glass ionomer as a pulp capping material has shown a poor clinical outcome and lack of reparative dentin formation (Hilton, 2009).

Bonding Agents

The use of resin bonding agents and adhesives for direct pulp capping were common in the 1990s. The recommendation for using bonding agents was made based on several animal studies which showed healing of the pulpal tissue when adhesives where applied directly on a mechanically exposed pulp. Several subsequent in vitro animal studies, however, reported poor pulpal healing when bacterial infection was induced into the exposed pulp.

When adhesives were used in human studies, the results showed poor seal to the cavity walls and inferior clinical outcomes. These results confirmed that adhesives will result in poor pulpal healing specially if used in cases with carious pulp exposure. In addition, resin adhesives are vasodilators which may compromise the healing of the pulp by increasing the bleeding. It was concluded in a systematic review that adhesives will result in chronic inflammation, and based on the recent findings, it is not suggested to use adhesives for direct pulp capping (Hilton, 2009; Schwartz et al., 1996).

Calcium Hydroxide

Calcium hydroxide (Ca(OH)₂) was for many years recognized as the “gold standard” for direct pulp capping procedures (Hilton, Ferracane, & Mancl, 2013). The material was introduced to dental practice in 1921, and since that time calcium hydroxide has been a very popular cavity liner. Its use in dentistry became very popular when a human study was published in 1930 (Mente,
Calcium hydroxide has the ability of solubilizing Bone Morphogenic Protein (BMP) and Transforming Growth Factor-Beta one (TBF- β1) from dentin. These proteins are responsible for stimulating pulp repair. This process explains the mechanism of action in direct pulp capping when calcium hydroxide is used (Hilton, 2009). Additionally, calcium hydroxide when used in pulp capping can reduce bacterial count in the cavity which also promotes reparative dentin formation (Hilton, 2009).

For many years, studies have shown that calcium hydroxide is superior to the previously discussed materials such as adhesives or glass ionomer. The outcome of pulp capping using calcium hydroxide was successful based on both short and long periods of follow up (Hilton, 2009). There are two main disadvantages of calcium hydroxide. First, the material can dissolve over time; therefore, it has been suggested to place a sealant over the calcium hydroxide layer (Hilton, 2009; Roberson et al., 2006). Second, studies have reported tunnel defects in the reparative dentin layer over the pulp (Hilton, 2009).

Mineral Trioxide Aggregate (MTA)

Mineral trioxide aggregate was developed and introduced to dentistry by Mahmoud Torabinejad in 1999, and it was mainly used as a cement in root canal therapy. MTA is composed of tricalcium silicate, dicalcium silicate and tricalcium aluminate, and some manufactures add bismuth oxide to enhance radiopacity of the material (Hilton, 2009). There are two different colors for MTA, white and grey (Torabinejad & Chivian, 1999), but applying grey MTA was found to darken the tooth structure.

MTA, according to several studies, has proven to have good biocompatibility in direct contact with
the pulp. Moreover, MTA prevents micro-leakage, and promotes regeneration of the tissue and provides better seal than calcium hydroxide (Hilton, 2009; Torabinejad & Chivian, 1999). The primary setting reaction of MTA produces calcium hydroxide which, as described above, enhances cell proliferation and accounts for the biocompatibility of the material. The antibacterial effect of MTA is due to its alkaline pH level. Furthermore, MTA enhances migration of hard tissue-producing cells (Parirokh & Torabinejad, 2010). When MTA was used in clinical trials as a direct pulp capping material, it showed comparable results to calcium hydroxide. The main disadvantage of MTA was the prolonged setting time when it was first introduced to clinical practice. However, new formulas of MTA showed the ability to accelerate the setting time (Hilton, 2009).

Many studies published in the past ten years compared the clinical outcome of MTA as a direct pulp capping material to that of calcium hydroxide. Some studies claimed that MTA can show better results in short-term studies (Hilton, 2009). However, a two year clinical study was published in 2013, and confirmed that MTA shows superior clinical results when compared to calcium hydroxide (Hilton et al., 2013). A systematic review and meta-analysis compared MTA to calcium hydroxide and concluded that MTA cases show less pulpal inflammation and enhanced reparative dentin formation (Li et al., 2015).

In recent years, the use of MTA or calcium hydroxide in direct pulp capping was one of the most arguable topics in dentistry. This systematic review aims to produce a consensus about MTA and calcium hydroxide in direct pulp capping using as the best available evidence. The objective of this comparative effectiveness approach is to better inform patients and other stakeholders in the clinical decision-making process.
2. Evidence-Based Dentistry

The American Dental Association (ADA) defines Evidence-Based dentistry as: “An approach to oral healthcare that requires the judicious integration of systematic assessments of clinically relevant scientific evidence, relating to the patient’s oral and medical condition and history, with the dentist’s clinical expertise and the patient’s treatment needs and preferences.” It is important to differentiate between evidence-based dentistry and dentistry based on the evidence. The evidence based research became recognized in the past few decades. This approach in dental research focuses on identifying and recognizing the best research evidence for any patient by engaging data generated using different research methods (F. Chiappelli et al., 2003).

In daily dental practice, it is important for the well-being of the patient to use the best-available evidence in choosing the appropriate treatment method or intervention. Evidence-based dentistry is a patient-centered research method. Dentists who are unfamiliar with evidence-based research may obtain misleading information regarding the effectiveness of an intervention from low strength of evidence sources such as case reports and case control studies (Fig. 2). Therefore, evidence-based dental research gives dentists the ability to better evaluate and select dental products. Dental care providers, insurance companies and policy makers must be informed about the best available evidence to succeed in making cost-effective decisions for patients or stakeholders (Francesco Chiappelli, 2014; F. Chiappelli et al., 2003).

There are two main domains of evidence based dentistry, the investigational component and the clinical mode. The investigational component includes comparative effectiveness and efficacy
research and analysis for practice (CEERAP). It is an essential step in evidence-based dentistry research as well as for posing the research question (PICO question). The clinical mode domain integrates (CEERAP) into the decision-making process. There are several agencies that aim to disseminate the best available evidence to dentists such as: The American Dental Association (ADA) and Agency for Healthcare Research and Quality (AHRQ) (Ajaj et al., 2012; Francesco Chiappelli, 2014).

The first step in the scientific process is to pose the question. The patient-centered research question should be formulated based on the individual patient needs and benefits. The research question should address:

- The Patient’s characteristics (P)
- The independent variables (I)
- That are under consideration or comparison (C)
- The outcome variable (O)
- Within planned time (T)
- In a projected experimental setting (S)

After formulating the question, keywords are obtained from the question and used to search for relevant studies. Next, inclusion and exclusion criteria are applied on these studies to obtain a bibliome. Then, assessment of the quality of the evidence and level of evidence is performed to ensure that the included studies comprise high level of evidence. The acceptable sampling process
assists in eliminating studies with the lowest level of evidence. Research synthesis combines the homogenous data from the accepted studies. Then, an overarching statistical analyses is performed by running a meta-analysis. Finally, the scientific process produces a consensus of the best available evidence in the form of a scientific review (Ajaj et al., 2012; Francesco Chiappelli, 2014).

There are two important issues that should be recognized for meta-analysis, which are homogeneity and bias. Lack of homogeneity in the studies will not allow performing the meta-analysis and produce statistical consensus. If there is homogeneity in a few studies, meta-analysis can be performed on theses subgroups, but that will affect the power, and produce non-significant statistical results. Bias could be a result of heterogeneity or due to publication bias, and the bias of publishing only significant results can affect the outcome of meta-analysis.

The purpose of the evidence-based research process is to ensure the development of information about the cost and effectiveness of interventions in clinical practice. An effort should be made by dentists and researchers to disseminate these reviews into clinical summaries (bioinformation dissemination) that can also be reviewed by patients and stakeholders. Health literacy involves gathering information regarding the efficacy and effectiveness of a certain intervention, and translating that knowledge into daily practice (Francesco Chiappelli, 2014).

3. Purpose of the Study

This comparative effectiveness review aims to produce a consensus for direct pulpal exposure cases of asymptomatic teeth in both male and female patients, and to discuss if Mineral Trioxide Aggregate shows superior clinical outcomes of pulpal healing in a minimum of a three month follow up compared to Calcium hydroxide in a clinical setting.
The components of the research question in this study are:

- **Population**: male and female patients with pulp exposure of permanent teeth and no signs or symptoms of pulpal inflammation.

- **Intervention**: Mineral Trioxide Aggregate.

- **Comparator**: Calcium Hydroxide.

- **Outcome**: Maintain vital pulpal tissue.

- **Timing**: Three months (follow up).

- **Setting**: Dental clinic.
Chapter 2

Methodology

1. Hypothesis

1.1 Null Hypothesis:

For direct pulp capping, Mineral trioxide Aggregate and Calcium Hydroxide show comparable and equivalent clinical outcomes.

1.2 Research Hypothesis

Mineral Trioxide Aggregate (MTA) is more effective than Calcium Hydroxide as a pulp medicament in cases of direct pulp capping.

2. Search Strategy Design

The search was conducted using four search engines in addition to the hand searching process. The process of searching for the relevant studies was performed using the keywords obtained from the PICOTS question and the analytical framework. The key questions in the analytical framework were also used. The following questions are:

- KQ1: Does MTA show enhanced pulpal healing?
- KQ2: What are the benefits of MTA in the process of reparative dentin formation?
- KQ3: Is MTA more cost effective per use?
- KQ4: Does MTA have higher clinical success rate in both short and long term?
- KQ5: In Cases treated with MTA for direct pulp exposure, did the patient receive the permanent restoration at the same appointment?

- KQ6: What are the adverse effects of using MTA for direct pulp capping?

- KQ7: Is the clinical outcome of MTA impacted by the type of exposure?

- KQ8: In cases treated with MTA what is the strength of evidence that the seal of the material to dentin can enhance the clinical outcomes?

The following keywords were obtained and used for the search:

- Pulp capping,
- Dental pulp capping,
- Direct pulp capping,
- Calcium Hydroxide,
- Dycal,
- Ca(OH)2,
- Mineral Trioxide Aggregate,
- MTA,
- GMTA,
- WMTA,
- ProRoot MTA.
2.1. Search Engines

The search engines that were used in the search process are:

ADA Center for Evidence-Based Dentistry

The search was performed on the Evidence-Based Data Base. Studies are categorized on the data base by the topic and all the relevant studies that were obtained from the data base were retrieved for reviewing and evaluation.

PubMed

The research strategy used on PubMed to search for relevant systematic reviews:

Pulp Capping AND (MTA OR Calcium Hyrdoxide) AND systematic reviews:(("Dental Pulp Capping"[Mesh] OR "pulp capping"[text word] OR "pulp cappings"[text word]) AND ("mineral trioxide aggregate"[Supplementary Concept] OR "MTA"[text word] OR "theracal"[text word] OR "fillapex"[text word] OR "mineral trioxide aggregate"[text word])) OR "Calcium Hydroxide"[Mesh]) AND (systematic[sb] OR Meta-Analysis[ptyp]).

The search strategy used on PubMed to search for relevant clinical trials:

((("Dental Pulp Capping"[Mesh] OR "pulp capping"[text word] OR "pulp cappings"[text word])) AND ("mineral trioxide aggregate" [Supplementary Concept] OR "MTA"[text word] OR "theracal"[text word] OR "fillapex"[text word] OR "mineral trioxide aggregate"[text word])) OR ("Calcium Hydroxide"[Mesh] OR "calcium hyrdoxide"[text word]) AND ("Clinical Trial "[Publication Type] OR "Randomized Controlled Trial "[Publication Type] OR "randomized"[tiab] OR "placebo"[tiab] OR "drug therapy"[sh] OR randomly[tiab] OR trial[tiab] OR groups[tiab]) NOT ("animals"[MeSH] NOT "humans"[MeSH]).
A similar search strategy was used to search for observational studies.

**Cochrane Library**

Searching in this data base requires using a unique strategy. The search strategy was built as:

#1 MeSH descriptor: [Dental Pulp Capping] explode all trees

#2 "pulp capping" or "pulp cappings"  (Word variations have been searched)

#3 #1 or #2

#4 "mineral trioxide aggregate" or "MTA" or "theracal" or "fillapex"  (Word variations have been searched)

#5 MeSH descriptor: [Calcium Hydroxide] explode all trees

#6 Calcium Hydroxide (Word variations have been searched)

#7 #4 or #5 or #6

#8 #3 and #7

**Web of Science**

The research strategy used on this database was similar to the previously explained strategy using the applicable keywords.
2.2. Hand Searching

The following three sources were selected for the hand searching process, which were limited to the previous five years.

1. The Journal of Endodontic (American Association of Endodontists)
3. WWW.CLINICALTRIALS.GOV

The results from all search engines and hand searching collected were done to determine their relevance, and the research process ended on April 30th 2016.

3. Determination of the Relevance

The initial research process resulted in 1233 studies which is summarized in figure (1). The first step in obtaining the bibliome is removing the duplicate then applying the inclusion and exclusion criteria as following:

3.1 Inclusion Criteria

- Clinical Trials
- Papers in English
- Adult patients
- Permanent teeth only
- Direct pulp Capping with MTA and Ca(OH)₂

3.2 Exclusion Criteria

- Primary teeth
- Indirect Pulp Capping
- Direct pulp capping with other materials (Glass Ionomer or adhesives for example)
- Teeth diagnose as Irreversible Pulpitis
- In vitro studies
- The total number of studies obtained after removing the duplicate and applying the inclusion and exclusion criteria was 32 studies.

3.3 Relevance to the PICOTS Question

The 32 studies were reviewed to determine the relevance to the proposed PICOTS question and confirm the pertinence to the aim of this study. The bibliome of the current study included 16 studies.

4. Measurements

4.1 Level of the Evidence

The studies included in the bibliome were reviewed and evaluated based on their level of evidence and following the criteria published by The Journal of Evidence-Based Dental Practice (Newman, Weyant, & Hujoel, 2007). Figure (2) explains the level of the evidence.

4.2 Quality of the Evidence

Two independent readers evaluated the quality of studies in the bibliome using well established instruments. Standardization of the two readers was performed by reviewing three studies for each instrument. Meetings were held to discuss any discrepancies in scoring of the papers using these instruments.

4.2.1 Quality of Systematic Reviews

AMSTAR, a measurement tool for the assessment of multiple systematic reviews, was introduced in 2007 to help evaluate the quality of systematic reviews. The instrument was revised in 2010 to
quantify the quality of systematic reviews using a checklist (Kung et al., 2010). The revised AMSTAR (R-AMSTAR) consists of the following eleven questions:

1. Was an “a priori” design provided?

2. Was there duplicate study selections and data extraction?

3. Was a comprehensive literature search performed?

4. Was the status of publication (i.e., grey literature) used as an inclusion criterion?

5. Was a list of studies (included and excluded) provided?

6. Were the characteristics of the included studies provided?

7. Was the scientific quality of the included studies assessed and documented?

8. Was the scientific quality of the included studies used appropriately in formulating the conclusion?

9. Were the methods used to combine the findings of studies appropriate?

10. Was the likelihood of publication bias assessed?

11. Was the conflict of interest included?

The scores for each question in the checklist range from 1 to 4 and the maximum score for a systematic review is 44.
4.2.2 Validating the Quality of the Evidence and Strength of Recommendation

The GRADE Working Group devolved an instrument to assess the quality of the evidence and the strength of recommendation. The Grading of Recommendation, Development, and Evaluation (GRADE) evaluate studies by looking at the study design, study quality, consistency and directness. The GRADE produced a qualitative statement using a scale to evaluate each section as high, moderate, low and very low.

The instrument was devolved and expanded to quantify the main two arms of the GRADE, quality of the evidence and strength of recommendation. The quantitative instrument is called Ex-Grade (Phi et al., 2012).

In the quality of evidence section, the revised risk of bias instrument was used (Barkhordarian et al., 2013), and for evaluating the strength of recommendation the following questions and criteria of scoring were used:

2. Are risk and affordability considered when given the recommendation for the intervention?

Criteria:

- Recognition of risk for the intervention is directly stated, or acknowledgement of risk can be inferred.

- Recognition of possible adverse effects post-intervention is directly stated, or acknowledgement of possible adverse effects post-intervention can be inferred.

- Recognition of cost for the intervention is directly stated, or approximate and/or relative cost for the intervention can be inferred.
• Recognition of affordability is directly stated or can be inferred

a. Fulfills 3 of the criteria=4

b. Fulfills 2 of the criteria=3

c. Fulfills 1 of the criteria=2

d. Fulfills 0 of the criteria=1

3. Are alternative recommendations given, if appropriate?

Criteria:

Alternative suggestions or recommendations were given with regards to risk during the intervention

• Alternative suggestions or recommendations were given with regards to possible adverse effects following the intervention

• Alternative suggestions or recommendations were given with regards to cost & affordability

• Explicitly states that no alternative recommendations are appropriate with regards to risk during the intervention

• Explicitly states that no alternative recommendations are appropriate with regards to possible adverse effects following the intervention
• Explicitly states that no alternative recommendations are appropriate with regards to cost & affordability

a. Fulfills 3 of the criteria=4

b. Fulfills 2 of the criteria=3

c. Fulfills 1 of the criteria=2

d. Fulfills 0 of the criteria=1

4. Is availability of resources for the population of interest taken into account prior to formulating the recommendation? [Is the recommendation practical for the population of interest?]

Criteria:

• Insurance coverage is available for the recommended intervention at hand [Some research on various insurance plans may need to be done]

• Other alternative funding aside from insurance is available for the recommended intervention at hand [Some research for alternative funding may need to be done]

• Resources in terms of equipment & supplies for the recommendation are easily accessible in clinical practice [This may require some prior knowledge of the equipments & supplies provided in the standard setting of the population of interest]

a. Fulfills 3 of the criteria=4
b. Fulfills 2 of the criteria=3  

c. Fulfills 1 of the criteria=2  

d. Fulfills 0 of the criteria=1  

5. Is a measureable guideline provided to monitor the intended outcome(s) of the recommendation?  
[Was there a method provided that can measure the effectiveness of the recommendations? How did they/will they measure the outcomes or results?]  

Criteria:  

- Method of monitoring the intended outcome of the recommendation is given  
- Method of monitoring the intended outcome can produce tangible data for the researcher  
- Method of analyzing the data produced from monitoring the intended outcome is provided  

a. Fulfills 3 of the criteria=4  

b. Fulfills 2 of the criteria=3  

c. Fulfills 1 of the criteria=2  

d. Fulfills 0 of the criteria=1  

6. Are the results of the intervention statistically significant?  

Criteria:
• Chosen methodology of the research is appropriate for the intended recommendation at hand

• Methodology of the research (e.g. methodology of the clinical trial, methodology of the systematic review, etc.) is executed properly & accurately

• Statistical analysis of the data shows statistical significance with p < 0.05

a. Fulfills 3 of the criteria=4

b. Fulfills 2 of the criteria=3

c. Fulfills 1 of the criteria=2

d. Fulfills 0 of the criteria=1

7. Are the results clinically significant?

Criteria:

For curative medicine/care, palliative medicine/care, or aesthetic/cosmetic care:

• The intervention alters the pathophysiology of the disease/issue in question

• The intervention can be realistically carried out & successfully executed in the clinical setting
• The time it takes for noticeable results to be seen post-intervention is reasonable taking into consideration the total cost of the intervention (Cost = monetary expenses & risk, both during the intervention & post-intervention)

For preventive medicine/care:

• The intervention does not alter the pathophysiology of the disease/issue in question

• The intervention does not induce another pathology aside from the disease/issue in question

• The intervention can be realistically carried out & successfully executed in the clinical setting

a. Fulfills 3 of the criteria=4

b. Fulfills 2 of the criteria=3

c. Fulfills 1 of the criteria=2

d. Fulfills 0 of the criteria=1

8. Is the patient likely to comply with the suggested recommendation?

• Minimal level of invasiveness to the patient

• Minimal level of side effects after the given intervention
- Benefits of the recommendation outweigh its total cost (Cost = monetary expenses & risk, both during the intervention & post-intervention)

  a. Fulfills 3 of the criteria = 4

  b. Fulfills 2 of the criteria = 3

  c. Fulfills 1 of the criteria = 2

  d. Fulfills 0 of the criteria = 1

5. Acceptable Sample Analysis

The acceptable sampling process was performed using the Medical Data Analysis System (MDAS). The acceptable sampling was completed in two separate steps, first for systematic reviews, then clinical trials and observational studies. Average scores of the two independent readers were transferred into MDAS and performed the Friedman statistical test of non-parametric variance. The Friedman test was used to identify homogeneity and exclude studies of low scores, and when the p value is less than 0.05 that indicates heterogeneous scores. Then the process is repeated after excluding the lowest scoring paper until the p value is above 0.05.
Chapter 3

Results

1. Search Results

The initial search for Systematic reviews, clinical trials and observational studies resulted in 1233 studies. These studies were obtained by hand searching three different sources and using four search engines. The search process started with removing the duplicate and then applying the inclusion and exclusion criteria. Thirty-two studies were reviewed and evaluated to their relevance to the PICOTS question. The final step resulted in a bibliome composed of 16 studies.

These studies were 7 clinical trials, 5 observational studies and 4 systematic reviews. Figure (1) shows the research process in summary of all the steps, which include systematic reviews and meta-analysis.


2. Direct Pulp Capping with Calcium Hydroxide or Mineral Trioxide Aggregate: A Meta-analysis (Li et al., 2015).


The Observational studies are:
1. Direct Pulp Capping with Mineral Trioxide Aggregate: An Observational Study (Bogen, 2008).

2. Outcome of Direct Pulp Capping with Mineral Trioxide Aggregate: A Prospective Study (Marques, Wesselink, & Shemesh, 2015).

3. Treatment Outcome of Mineral Trioxide Aggregate or Calcium Hydroxide Direct Pulp Capping: Long-term Results (Mente et al., 2014).

4. Mineral Trioxide Aggregate or Calcium Hydroxide Direct Pulp Capping: An Analysis of the Clinical Treatment Outcome (Mente, Geletneky, Ohle, Koch, Friedrich Ding, et al., 2010).


The following clinical trials were obtained in the bibliome

1. Comparison of CaOH with MTA for Direct Pulp Capping: A PBRN Randomized Clinical Trial (Hilton et al., 2013).

2. Evaluation of two mineral trioxide aggregate compounds as pulp-capping agents in human teeth (Accorinte et al., 2009).


4. A Randomized Controlled Study of the Use of ProRoot Mineral Trioxide Aggregate and Endocem as Direct Pulp Capping Materials: 3-month versus 1-year Outcomes (Jang et al., 2015).
5. Clinical Outcomes for Teeth Treated with Electrospun Poly(epsilon-caprolactone) Fiber Meshes/Mineral Trioxide Aggregate Direct Pulp Capping (Lee et al., 2015).


7. Histological, ultrastructural and quantitative investigations on the response of healthy human pulps to experimental capping with mineral trioxide aggregate: a randomized controlled trial (Nair, Duncan, Pitt Ford, & Luder, 2009).

2. Assessment of Systematic Reviews and Meta-Analysis Studies

R-AMSTAR was used to evaluate the quality of the systematic reviews. Pilot systematic review obtained to standardize the two independent readers and meetings were held to discuss any discrepancies in scoring the pilot study and the first two papers. Table (1) shows the average score for each systematic review or meta-analysis.

The table contains scores, standard deviation and marginal mean. These scores were transferred to (MDAS) for the acceptable sampling process. Friedman’s test for homogeneity was used for the acceptable sampling, and when the p value is below 0.05 that indicated a heterogeneous result. One systematic review was excluded during the process and the following papers were accepted:

1. Direct Pulp Capping with Calcium Hydroxide or Mineral Trioxide Aggregate: A Meta-analysis (Li et al., 2015).

2. Clinical outcome of direct pulp capping with MTA or calcium hydroxide: A systematic review and meta-analysis (Zhu et al., 2015).

3. Assessment of Clinical Trials and Observational Studies

Observational studies and clinical trials were evaluated using the Ex-GRADE instrument, which has two main arms: quality of the evidence and strength of recommendation. The revised risk of bias instrument was used in the first arm of Ex-GRADE to evaluate the quality of the evidence. The revised risk of bias instrument has four domains to evaluate design, consistency, directness and precision.

The second arm of Ex-GRADE has seven questions to evaluate the strength of recommendation. Tables (2) and (3) shows the scores for observational studies and clinical trials. Friedman’s test was used for the acceptable sampling to determine homogeneity and exclude low scoring studies.

The following clinical trials were accepted:

1. Comparison of CaOH with MTA for Direct Pulp Capping: A PBRN Randomized Clinical Trial (Hilton et al., 2013).

2. Clinical Outcomes for Teeth Treated with Electrospun Poly(epsilon-caprolactone) Fiber Meshes/Mineral Trioxide Aggregate Direct Pulp Capping (Lee et al., 2015).

The accepted observational studies were:

1. Direct Pulp Capping with Mineral Trioxide Aggregate: An Observational Study (Bogen, 2008).
2. Treatment Outcome of Mineral Trioxide Aggregate or Calcium Hydroxide Direct Pulp Capping: Long-term Results (Mente et al., 2014).

3. Mineral Trioxide Aggregate or Calcium Hydroxide Direct Pulp Capping: An Analysis of the Clinical Treatment Outcome (Mente, Geletneky, Ohle, Koch, Friedrich Ding, et al., 2010)


4. Data Extraction

Accepted studies were reviewed thoroughly for data extraction. Key questions were used as a guide during the data extraction process. In addition, PICOTS question and the analytical framework used to choose the elements of data in each study were also used. Table (4) shows the summery of data extraction for clinical trials and observational studies. The table shows the summery of the data extraction by identifying the study design, intervention, comparator (if applicable), sample size and period of follow up.

For the systematic reviews and meta-analysis, data extraction was performed, and a concise summary statement were obtained from each study. These statements are crucial for the qualitative consensus.
Chapter 4

Discussion

1. Interpretation

The acceptable sampling process yielded nine studies after eliminating papers that had low scores by the two readers while evaluating the quality of the evidence. The aim of this study was to perform a meta-analysis by obtaining and analyzing the best available evidence. A Meta-analysis requires obtaining homogeneous data and then applying statistical procedures integrating results from independent studies and produce a statistical summary.

The data obtained from the accepted studies shows no unified manner to measure the outcome of the direct pulp capping procedure. Different criteria were used in each study to evaluate the success rate of direct pulp capping procedure or reporting failure. Some studies used the clinical diagnosis based on the signs and symptoms as an indicator for success, where in other studies radiographs were assessed to report failed pulp capping. A Meta-analysis cannot be performed on a heterogeneous data.

2. Qualitative Analysis

2.1 Li et al Study

In this meta-analysis thirteen studies were included for the quantitative synthesis in comparing MTA to calcium hydroxide. Five studies of 931 teeth comparing the success rate were included in a meta-analysis and indicated that MTA significantly has higher success rate. Inflammatory response was assessed in nine studies out of the thirteen included, and MTA showed significantly less inflammatory response. MTA also showed better outcomes when comparing the dentin bridge
formation. The author concluded that “MTA has a higher success rate and results in less inflammatory response and more predictable hard denting bridge formation than CH” (Li et al., 2015).

2.2 Zhu et al Study
This is a systematic review to compare the effect of MTA and calcium hydroxide as a direct pulp capping. Four studies were included in this systematic review and the total number of teeth in these studies was 501. The study showed that MTA is superior to calcium hydroxide when used for direct pulp capping. The difference in success rate was statically significant. The author suggested that larger randomized trials are needed (Zhu et al., 2015).

2.3 Aguilar et al Study
This study was performed to demonstrate the success rate of direct pulp capping, partial pulpotomy and full pulpotomy. Data extracted for the direct pulp capping showed that there was superiority of MTA over calcium hydroxide when an indirect comparison was done for the weighted pooled success rate (Aguilar & Linsuwanont, 2011).

2.4 Hilton et al Study
This is a large randomized clinical trial conducted in a practice-based research group and cases were followed up for two years. Three hundred and seventy-six patients were enrolled in this study and MTA was used in 138 teeth, where calcium hydroxide was used in 175 teeth. Primarily, failure was recorded when a clinical recommendation for root canal treatment or extraction was made. Secondary analysis recorded a failure if radiolucency was detected in a radiograph. Forty-five failed cases were reported for calcium hydroxide and twenty-five cases for MTA. The study concluded that MTA is superior in performance as a direct pulp capping when compared to
calcium hydroxide (Hilton et al., 2013).

2.5 Lee et al Study

This is a clinical trial performed in a short period of a three-month follow-up. Sixty patients were included and teeth were divided into four groups, where two groups of less than 1 mm of exposure and the other two had exposure of 1-1.5 mm. Thirty teeth of two different exposures were treated with MTA direct pulp capping and the other two groups of thirty teeth received PCL-FM/MTA. No failures were reported in the MTA group but that may be affected by the short period of the follow up (Lee et al., 2015).

2.6 Bogen Et Al

Thirty-seven patients were included in this cohort study with a total of 49 teeth treated with MTA. The follow period ranges from 1 to 9 years and the mean age of patients was 16.6 years. The pulpal survival after pulp capping of these cases was 97.96% (one failure). The outcome of the pulp capping was measured by evaluating patient's self-reports, clinical cold testing and periapical radiographs. The study concluded that “MTA can be a reliable pulp-capping material on direct carious exposures in permanent teeth when a two-visit treatment protocol is observed” (Bogen, 2008).

2.7 Mente et al Study (2014)

This observational study involved 282 patients with 229 teeth treated with either MTA or calcium hydroxide. The failure rate was higher in the cases treated with calcium hydroxide. The treatment outcome was reported as a failure based on clinical and radiographic findings. The result of the study supports the use of MTA in direct pulp capping based on a long term evaluation. The study suggested that the placement of the permanent restoration at the same appointment is an important
factor for better clinical outcomes (Mente et al., 2014).

2.8 Mente et al Study (2010)
This cohort study aimed to compare the outcome of pulp capping using MTA and calcium hydroxide. Fifty-three cases were treated with calcium hydroxide, and failure was detected in 21 teeth, while MTA was used in 69 teeth and failure reported for 15 cases. Assessment of the outcome based on the clinical and radiographic findings. Two examiners performed the clinical and radiographic evaluation, and follow up visits were performed between 12-80 months (Mente, Geletneky, Ohle, Koch, Friedrich Ding, et al., 2010).

2.9 Cho et al Study
In this study, 175 patients were included who received pulp capping using MTA and calcium hydroxide between 2007 and 2010. Failure was indicated in the recall visit if the tooth received root canal treatment. In addition, the presence of pulp necrosis and apical periodontitis was reported as a failure as well as spontaneous pain or lingering pain to thermal test. The authors suggested in the conclusion that MTA is a better choice for direct pulp capping (Cho et al., 2013).

3. Limitations

3.1 Limitations of Previous Studies
The research process of this study showed that there are limited clinical trials addressing the topic of direct pulp capping. Many of the clinical trials are conducted on teeth scheduled for extraction and the outcomes are measured based on histological evaluation and assessment. Most of these studies had a short period of follow ups. In addition, the histological evaluation results will not be homogeneous with the clinical outcomes in the patient’s mouth. There was only one clinical trial
included in the bibliome (Hilton et al., 2013) that produced long term evaluation of MTA and that represents a deficiency in the field.

Among all the studies included in the bibliome, there is no unified method to evaluate the success of direct pulp capping. In addition, there is a lack of homogeneity in defining successful pulp capping procedures. Clinical studies showed different methods in evaluating the clinical outcome based on clinical examination of the signs and symptoms, radiographic analysis of lesions or histological assessment of reparative dentin formation. Evaluation of the outcome resulted in heterogeneous data due to discrepancies between the studies. This in turn prevented us from performing overarching statistical analysis.

3.2 Limitations of the Current Study

The number of studies accepted was limited due to the restriction inclusion criteria of the current study. For instance, a small number of studies were accepted based on evaluating the quality of evidence. The research process was limited to studies published in the English language and any study after April 30th of 2016 was not involved. Researching for studies with a three months minimum recall evaluation affected the total number of included studies. In addition, the hand searching was restricted to the previous five years of publication dates. Finally, The PICOTS question was focused on traditional MTA, and currently there are studies that compare the outcome of new formula MTA, which may be discussed in a future project.

4. Conclusion and Recommendation

4.1 Conclusion

Calcium hydroxide showed some success in direct pulp capping, but the results from the studies included in this analysis verify that the outcomes of calcium hydroxide are inferior to MTA.
Accordingly, MTA showed a higher success rate within each study, reduced pulpal inflammation, and had more reparative dentin formation. Inconsistency in the research protocol among clinical studies did not allow performing meta-analysis and did not produce statistical analysis. Qualitative consensus of the research confirmed our hypothesis that favors MTA for direct pulp capping, and based on the best available evidence, there is an assertive agreement on the superiority of Mineral Trioxide Aggregate over calcium hydroxide when used as a direct pulp capping material. The superiority of MTA was confirmed in short and long follow up periods.

4.2 Research Recommendation

There is a need for more controlled clinical trials in the field to assess pulp capping materials in both long and short term periods of evaluation. In fact, these clinical studies should produce homogenous results by using common research protocols. Standardization of the research protocol will help in obtaining homogenous results from clinical, radiographic and histological examinations. It is important to produce critical summaries from the relevant studies and disseminate the results to dentist, patients and other stakeholders.

4.3 Clinical Recommendation

Dentists should be familiar with the scientific research synthesis and use the best available evidence for the benefits of their patients. This review confirms that direct pulp capping can be effective conservative approach to maintain the vitality of dental pulp tissue, and losing the vitality of the pulp may lead to root canal therapy or extraction, which will affect the oral health of the patient as well as their economic status. This is a cost-effective approach that benefits the patient and should be addressed in the decision-making process. This review confirms the superiority of
MTA as a direct pulp capping material, which is important knowledge to be disseminated to patients and other stakeholders.

4.4 Practical Implication

Currently, patient centered health care is developing and more dentists are interested in establishing evidence-based dental practice. The results of this systematic review should be formulated to be accessible by dentists, insurance companies, policy makers and stakeholders, and the consensus and recommendation of this review should be translated in a manner that is easy to be disseminated by interested patients. Table (6) shows a patient-friendly summary of this systematic review.
Figure 1: Summary of articles selection process

- PubMed
- Cochrane Library
- ADA EBD
- Web of Science
- Hand Search

From All search Engines → N=1233
Duplicate Removal → N=1157
Inclusion/Exclusion → N=639
PICOTS → N=32
Bibliome → N=16
Figure 2: Level of evidence
Figure 3: Analytical framework

- Patients with pulp exposure
  - Subgroups:
    - Permanent teeth
    - Asymptomatic pulp
    - Pulp exposure (caries, traumatic, mechanical)

- Adverse effect:
  - Long setting time
  - Discoloration
  - Cost
  - Difficult handling characteristics

- MTA
  - No signs or symptoms of pulpal inflammation or necrosis
  - No pain or discomfort

- Healing of pulpal tissue
  - Formation of reparative dentin
  - No clinical or radiographic sign of inflammation

KQ1, KQ2, KQ4, KQ8
Table 1: The average scores, means and standard deviation using R-AMSTAR instrument

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Table 2: The average scores, means and standard deviation using EX-GRADE for clinical trials

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Table 3: The average scores, means and standard deviation using Ex-GRADE for observational studies

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<td>0.4472136</td>
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<td>0.54772256</td>
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<tr>
<td>Marginal Mean</td>
<td>39</td>
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<td>3</td>
<td>3.7</td>
<td>32</td>
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<td>4</td>
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<td>38</td>
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</table>
Table 4: Data extraction summary table for Clinical trials and observational studies

<table>
<thead>
<tr>
<th>Name of the Author/Year</th>
<th>Study design</th>
<th>Number of patients enrolled</th>
<th>Age</th>
<th>Number of teeth</th>
<th>Cases treated with MTA</th>
<th>Cases treated with CaOH</th>
<th>Outcome for CaOH</th>
<th>Outcome For MTA</th>
<th>Follow up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hilton et al 2013</td>
<td>RCT</td>
<td>376</td>
<td>7 years and older</td>
<td>358</td>
<td>138</td>
<td>175</td>
<td>45 failed</td>
<td>25 failed</td>
<td>Up to 2 years (median 12.8 months)</td>
</tr>
<tr>
<td>Lee et al 2015</td>
<td>RCT</td>
<td>60</td>
<td>12-68</td>
<td>60</td>
<td>30</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>No failure</td>
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<tr>
<td>Bogen et al</td>
<td>Cohort study</td>
<td>37</td>
<td>Mean 16.6 years</td>
<td>49</td>
<td>49</td>
<td>-</td>
<td>-</td>
<td>One failure (survival of the pulp 97.96%)</td>
<td>1-9 years</td>
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<tr>
<td>Mente et al 2014</td>
<td>Cohort study</td>
<td>282</td>
<td>7-78</td>
<td>229</td>
<td>170</td>
<td>59</td>
<td>24 failed</td>
<td>33 failed</td>
<td>Up to 10 years</td>
</tr>
<tr>
<td>Mente et al 2010</td>
<td>Cohort study</td>
<td>108</td>
<td>8-78</td>
<td>122</td>
<td>69</td>
<td>53</td>
<td>21 failed</td>
<td>15 failed</td>
<td>12-80 months</td>
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<tr>
<td>Cho et al 2013</td>
<td>Cohort study</td>
<td>175</td>
<td>175</td>
<td>70</td>
<td>105</td>
<td>30 failed</td>
<td>7 failed</td>
<td>Median follow up 11.1 months</td>
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Table 5: The Inter-rater reliability

<table>
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<tbody>
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<td>1.00904</td>
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<td>Paper2</td>
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<td>18</td>
<td>1.09604</td>
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Table 6: Summary for patients and stakeholders

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>Quality of the evidence</th>
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<tbody>
<tr>
<td><strong>Pulp Capping</strong></td>
<td></td>
</tr>
<tr>
<td>The best available evidence confirms that direct pulp capping can be effective conservative approach to maintain the vitality of dental pulp tissue and avoid root canal treatment.</td>
<td>strong</td>
</tr>
<tr>
<td><strong>Material</strong></td>
<td></td>
</tr>
<tr>
<td>Mineral Trioxide Aggregate (MTA) is a cost effective material that shows better clinical outcomes in pulp capping compared to calcium hydroxide.</td>
<td>strong</td>
</tr>
</tbody>
</table>
References


8. Chiappelli, F. (2014). *Fundamentals of evidence-based health care and translational science* (pp. XXVII, 394 p. 357 illus., 329 illus. in color). Retrieved from [http://dx.doi.org/10.1007/978-3-642-41857-0](http://dx.doi.org/10.1007/978-3-642-41857-0)


