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Pulpotomy as an alternative treatment for posterior permanent mature teeth with irreversible pulpitis: a systematic review

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ABBREVIATIONS

AAE- American Association of Endodontics

Acta Odontol Scand- Acta Odontológica Scandinavica

CEM- Calcium Enriched Mixture

CET- Conventional Endodontic Treatment

CH- Calcium Hydroxide

Clin Oral Invest- Clinical Oral Investigations

Inter Endod J- International Endodontic Journal

IRM- intermediate Restorative material

JCD- Journal of Conservative Dentistry

J Endod - Journal of Endodontics

LOE- Level of Evidence

MTA- Mineral Trioxide Aggregate

PAI- Periapical Index

RCT-Randomized Clinical Trial

VPT- Vital Pulp Therapy

ABSTRACT

Introduction: Irreversible pulpitis in mature teeth is traditionally an indication for Conventional Endodontic Treatment (CET). Recent advances in pulp biology showed that teeth with carious lesions and symptomology matching irreversible pulpitis diagnosis, present inflammation limited to the coronal tissue near the carious lesions, while root canal pulp was healthy and normal. Pulpotomy procedures have been used to manage cariously exposed mature teeth without signs of irreversible pulpitis and nowadays some clinicians are testing this approach to treat permanent mature teeth with symptoms compatible with irreversibility.

The aim of this study is to review the treatment outcome of posterior definitive mature teeth with irreversible pulpitis submitted to pulpotomy as an alternative to CET.

Materials and Methods: To answer the PICO question “Could posterior mature permanent teeth diagnosed with irreversible pulpitis treated by pulpotomy (full or partial) expect an outcome (clinical and radiographic) similar to conventional endodontic treatment (pulpectomy)?”, a searching strategy was performed, independently by 2 reviewers, on PUBMED/Medline and EMBASE databases. The quality assessment of studies which resulted after full reading was based on Cochrane Collaboration Risk of Bias Tool and on ROBIS-I tool. Evidence level of studies was achieved based on Oxford Centre of Evidence Based Medicine.

Results: 15 articles resulted from the search on primary databases for full reading. Inclusion and exclusion criteria were applied and resulted in 10 articles. After quality assessment 8 studies were included in this systematic review (5 randomized clinical trials and 3 prospective cohort studies). The studies were presented in tables by study design and their characteristics were represented (sample size, age range, type of treatment and material, recall rate, follow-up, success rate and evidence level).

Conclusions: This systematic review finds studies with high level of evidence which reported high success rate to this procedure and this approach seems a viable alternative treatment to CET. The study with longer follow-up present a low recall rate and its evidence level is lower than the other included studies. The majority of studies only presented 1-year follow-up, therefore more studies with longer follow-up and with high recall rate are necessary to strengthen the evidence to accept this treatment as a viable alternative to CET.

Key-Words

Irreversible pulpitis; Pulpotomy; Bioceramic Materials; Vital Pulp Therapy.

INTRODUCTION

1. Pulp Diagnosis and Histologic relationship

Various classification systems are available to designate the health pulp states and the progression of pathologic alterations of the pulp tissue (1). The clinical state in which the pulp is symptom-free and normally responsive to pulp testing is defined, according to American Association of Endodontics - The Glossary of Endodontic Terms, as "*normal pulp*". Clinically, normal pulp is equivalent to vital asymptomatic or healthy pulp. Reversible pulpitis, irreversible pulpitis and pulp necrosis are also included in this terminology system based on clinical assessment of the teeth (2).

Traditionally, symptomatology and clinical tests results have been widely used and accepted as indicators of the inflammatory status of the pulp (1, 3, 4). Irreversible pulpitis was described by Anderson *et al.* in 1981 as a prolonged pain after clinical tests (percussive stimuli, thermal, electrical tests) (5). This is a widely accepted classification system of pulpitis and is also based on the expected outcome of its treatment. Therefore, pulpitis is classified as "reversible" when clinicians judgment is that pulp can predictably return to normal condition after removing the irritant stimulus and it's classified as "irreversible" when pulp condition is considered to have very little probability to be reverted to normal only by removal of the irritants (4, 6). Nevertheless, classical studies failed to find a reliable correlation between clinical diagnosis and the histopathologic findings observed in studied teeth (1, 3, 7). Consequently, the possibility of clinicians to accurately determine if a pulp can be saved or not based on the assessment of patients report of symptoms of pain has been challenged in recent years (1, 4).

A recent histologic study allowed a new insight into this issue, revealing a high correlation between clinical diagnosis of normal pulp and reversible pulpitis, with 96,6% of the assessed cases matching histologic condition. Notwithstanding, in the same study, teeth diagnosed with irreversible pulpitis showed a lower correlation with histopathological findings (84,4%). In those teeth, the coronal pulp tissue near the carious lesions showed morphologic inflammatory changes, as hyperemia with apparently empty spaces in a reduced odontoblast layer and scattered chronic inflammatory cells, localized to specific areas and it was frequent to observe uninflamed pulp tissue with normal architecture in the contralateral pulp horn (4). The presence of lingering pain after a stimulus, can be synonymous of irreversible pulpitis but may not necessarily correspond to an irreversible inflammation of the entire pulp (7-13). Interestingly, those teeth evidence root canal pulp in healthy condition and viable without inflammatory changes (4).

Recent scientific evidence supports the regenerative potential of pulpo-dentinal complex of teeth with irreversible pulpitis (14, 15) which challenges current classifications for pulp inflammation, because it shows that with proper intervention, teeth with extensive pulp inflammation can be treated by the removal of affected tissue and maintaining the vitality of the remaining pulp. Clinical symptoms (spontaneous or severe preoperative pain) or deep carious lesions don't always indicate that pulp cannot be capable of repair (16).

This undermines the rationale for use the term "irreversible", as it condemns the pulp, and fostered the proposal of a new diagnostical system for assessing pulpitis and subsequent treatment needs by Wolters *et al.* 2017, to highlight the healing potential of the pulp (8). These authors propose to change the criteria for clinical diagnosis of (ir)reversible pulpitis and suggest an expansion of the diagnostic categories of pulp inflammation to allow a rapport with minimally invasive treatments, in which the extensively inflamed tissue is removed and uninflamed tissue is preserved to keep the potential to heal. This new classification proposal establishes 4 levels of pulp inflammation, starting with initial, progressing to mild and then to moderate and severe. In this new vision, teeth with mild pulpitis present heightened and lengthened reaction to cold, warmth and sweet stimuli, which can last up to 20 seconds but then disappear. Severe pulpitis is associated with heightened and prolonged reaction to cold stimuli, which can persist for minutes, and possibly percussion sensitivity. The suggested treatment for this condition, depending on the intraoperative findings, is partial or full coronal pulpotomy. Even for teeth with severe pulpitis, characterized by spontaneous pain and clear reaction to cold stimuli, and often sharp to dull throbbing pain, these authors indicate full pulpotomy if bleeding control can be achieved. If not, clinicians are encouraged to remove the inflamed tissue inside the root canal, until finding uninflamed tissue, even if it takes going up to 4 mm from the apex, and then performing the biomaterial capping procedure (8).

All the recent developments in our understanding of pulp biology and response of the pulp-dentin complex to the release of intrinsic growth factors and bioactive materials are opening new perspectives and hope in the regenerative potential of the pulp (4, 8). For those reasons, less invasive approaches to the conventional endodontic treatment need to be explored (17), in order to achieve time and cost saving for the patient and society, better patient compliance and a long-term prognosis for retaining the natural teeth (8).

2. Pulp Therapies

The conventional and most widely accepted treatment for irreversible pulpitis, in permanent teeth, is the conventional endodontic treatment (CET), also known as root canal therapy or

pulpectomy. According to the AAE glossary of endodontic terms pulpectomy is defined as the complete (coronal and radicular) removal of the vital tissue (2).

CET has been accepted as the standard of care for irreversible pulpitis affecting permanent teeth with effectiveness in rapid control of pain and excellent long-term outcome. Nevertheless, it is a treatment with some limitations: may require multiple appointments, demand a high level of training and clinical skills (specifically in molar teeth), involves the use of high technological equipment and is expensive (18). Therefore, in some countries, low-income patients, with limited access to specialist care or uninsured became excluded from the possibility of retaining teeth affected by pulpitis and extraction is the unique treatment option, jeopardizing function and quality of life (18, 19).

Recent advances in pulp biology and physiology allowed a new vision of the degenerative changes that occur in pulp tissue undergoing progressive inflammatory pathology. Particular attention has been attributed to study pulp tissue regeneration to maintain pulp vitality using Vital Pulp Therapies (VPT), also known as Minimal Invasive Endodontic Treatment to approach teeth diagnosed with irreversible pulpitis (8, 19, 20). VPT is a general concept, which consists in a whole range of therapies to preserve healthy status of tooth and includes pulp capping (direct or indirect) and also pulpotomy (partial or complete) (16, 19, 21, 22).

In comparison to CET, this treatment requires less technique sensibility, is cheaper, more conservative and may eventually be performed at a good standard of quality level by the General Dentists (9, 15, 23).

2.1 Pulpotomy procedure

Pulpotomy is nowadays defined, according to AAE - The Glossary of Endodontic terms, as the removal of the coronal portion and the vitality of the remaining radicular portion is preserved (2).

The principle of pulpotomy procedure, as above referred, is maintaining the tooth vitality, removing infected/inflamed tissue and leaving healthy and vital tissue behind. Furthermore, this minimal invasive endodontic treatment has some potential advantages, such as, saving the tooth structure and consequently increasing tooth survival, reducing symptomatology (pain and discomfort) for the patient, simplifying treatment procedures, reducing costs for patients and preserving the immunological functions and proprioceptive defensive mechanisms of the remaining pulp (8, 24).

Pulpotomy was firstly advocated by Cvek, in 1978, when performing treatment of 60 permanent incisors with complicated crown fracture, and after, in 1993 to approach 37 posterior teeth with deep carious lesions and exposed pulps (25, 26). Cvek pulpotomy procedure consist in

removal of 2-3mm of pulp and dentin near the pulp exposure site (25-27). The outcome reported for this treatment after complicated crown fractures was 96% success rate after 31 months (mean) and 93,5% for cariously exposed teeth without clinical and radiographic signs and symptoms before the treatment and 66,7% for teeth with previous carious lesions and such symptoms after 24 months (25, 26).

Pulpotomy treatment can be total (also known as coronal or full) and partial (also known as miniature or Cvek pulpotomy). Total pulpotomy consists in removing the coronal pulp and has been considered as a definitive treatment to manage carious pulp exposure for primary teeth (28) and cariously exposed immature permanent teeth (29) with signs and symptoms of reversible or irreversible pulpitis (14, 26) and recently extended to mature teeth with reversible and irreversible pulpitis (9, 11-13, 16, 21, 22, 30-32). Partial pulpotomy consists in the removal of pulp tissue and dentin localized near the exposed area of the pulp (thickness removal advocated ranges from 1 to 3mm) (13, 25), and it is has been indicated to treat permanent teeth (traumatically and cariously exposed) with or without previous signs of reversible or irreversible pulpitis (18, 25, 26, 28, 33, 34). If the treatment is performed in a tooth with caries, first step is the complete removal of decayed hard tissue, disinfection of the cavity and then pulp can be exposed (26). After pulp exposure, a wide range of techniques have been advocated to remove the inflamed pulp tissue and bleeding control agents and solutions also differ from one study to another. Time to achieve bleeding control is considered a sign of the extent of pulp inflammation (35) and the maximum compatible with good success expectation is not yet defined, but a study referred 10 minutes as a maximum (35) .

The material used to remove inflamed tissue usually is a diamond round bur in a high-speed handpiece with copious irrigation but in some studies copious irrigation was not referred. Laser may also be used for this purpose (36). To control bleeding, different irrigation solutions are indicated (sterile saline solution or sodium hypochlorite with different concentrations), and the use of wet or moistened cotton pellets also are proposed (chlorhexidine 0,2% or NaOCl 2,5%) (9-13, 16, 21, 27, 30-32). In a recent study, moistened cotton pellets with 2,5% NaOCl were used with a dry pellet on top (16).

Hemorrhage control is critical for the success of any pulp capping treatment, after amputation of the infected pulp, if bleeding time is prolonged (the time limit is different between the studies), the residual pulp may be still inflamed and the healing potential be restricted (35). When it happens, CET will be the alternative and more effective treatment choice.(14)

During the last decades, the presence of prolonged and spontaneous pain was a contraindication to VPT in permanent mature teeth (28). Scientific community defended that pulp may reduce the defense ability (poor blood supply) in older patients. However, recent studies suggested pulpotomy as a treatment option to permanent mature teeth diagnosed with

irreversible pulpitis and age was not found as a relevant prognostic factor (8, 24). Moreover, if this conservative treatment fails, more treatments are available and can be subsequently considered: CET, apical surgery or extraction (8).

3. Treatment Outcomes

Swift *et al* in 2003 established the requirements for a successful vital pulp therapy, which includes: removal of all inflamed pulp; proper control of hemorrhage; application of non-toxic capping material; seal out bacteria by capping material and a quality restoration to avoid coronal microleakage (27).

To assess the outcome of VPT various success criteria have been proposed. European Society of Endodontology, in 2006, published quality guidelines for this endodontic treatment and suggest: normal response to pulp sensitivity tests (when feasible), absence of pain and other symptomology, radiographic evidence of dentinal bridge formation in teeth with opened apices and absence of radiographic internal resorption signs and apical periodontitis (37).

The terminology usually used to classify the pulpotomy outcome was binary. Terms “success” or “failure” were used without any alternative. The inconsistent definition of “success” and the use of different outcome criteria is one of the main causes of variability of reported outcomes in different follow-up studies (38). Therefore, Zanini *et al* proposed new criteria for evaluation of the outcome of pulpotomy, including 3 possible categories: “success”, “uncertain outcome” or “failure”. Criteria proposed for the evaluation were clinical and radiographic: functional and non-infected teeth were included in clinical outcome and periapical index was included in radiographic outcome (scoring system for radiographic assessment of apical periodontitis) (38).

In these criteria, “uncertain” is necessary to define recent pulpotomies which are not possible to assess the treatment outcome or in pulpotomy’s cases that diagnosis criteria aren’t possible to be verified (38). “Success”, in the majority of studies, is used requiring a combination of **clinical** and **radiographic** success (39, 40).

3.1 Clinical outcome

Clinical outcome measures have been widely used to assess the state of endodontic treated teeth. When signs or symptoms are present, such as swelling, sinus tract and tenderness to percussion and palpation, presence of mobility or positive periodontal probing, the endodontic treatment is classified as a “failure”, as they are an expression of an endodontic infection, but are not specific to apical periodontitis. “Success” is defined as the absence of the signs or symptoms above referred (39, 40). Normal response to pulp thermal and electrical tests is a

“success” signal but in pulpotomized teeth the accuracy of pulp tests may be limited because of the distance of remaining vital pulp tissue from the tooth surface (37, 38). Zanini *et al* proposed as “success” criteria the lack of pain declaration, presence of a functional tooth and a restoration with adequate properties to prevent coronal microleakage (38).

3.2 Radiographic outcome

The aim of radiographic evaluation is to compare possible periapical changes between two assessment dates (38). Usually, radiographic “success” is defined when tooth surrounding tissues do not exhibit radiolucency and are classified as having healed. When tissues exhibit radiolucency can be classified as “healing” or “failure”: It is classified as “failure” or “disease” with presence of radiolucency that persisted without changes. When radiolucency is more reduced combined with clinical normalcy can be interpreted as a suggestion of “healing” (39, 40).

After pulpotomy procedure, mineralization activity and internal resorption can also be evaluated: it is a “success” when radiopaque area is detected under pulp capping material and canal obliteration is not present. Canal obliteration, in the majority of studies, is considered as a “failure” criteria, but it is not a real absence of pulp vitality, it could reflect either actual or past vitality of the pulp (38).

Many studies showed radiographic outcome based on Modified Strindberg criteria (9-12), other studies based on Periapical Index (PAI) (13, 16, 31, 32). Zanini’s proposed outcome assessment, includes radiographic criteria based on PAI, considering success when Periapical Index is <3 (PAI=1 – Periapical bone is normal; PAI=2 – Presence of small changes in bone structure but not pathognomonic for apical periodontitis). The PAI has 5 scores, being the scores 3, 4 and 5 considered as radiographic failures (38). Strindberg criteria included 3 different radiographic outcomes: healed, healing (reduction of the previous lesion) or failure (41).

4. Pulp Capping materials

Historically, calcium hydroxide (CH) was the most popular material for VPT (13, 24, 27, 28, 35). CH materials showed instability, are prone to resorption and weak to microleakage prevention (many imperfections and tunnel defects) (42), as well as easy to dissolve and ineffective to adhere closely to dentin (24).

Nowadays, several studies suggest bioceramic materials as a more favorable option. During the last two decades, notable progresses have been made in the field of bioceramic biomaterials for endodontic treatment (43).

Mineral Trioxide Aggregate (MTA) (Dentsply -Tulsa Dental, Johnson City, USA), a Portland cement, became recognized as the gold-standard bioceramic material for a variety of clinical conditions and is the most extensively studied cement in this group (22). It was the first bioceramic endodontic material introduced as an endodontic repair material (24). It contains tricalcium silicate, dicalcium silicate, tricalcium aluminate, bismuth oxide (insoluble radiopaque substance) and calcium sulfate dehydrate (24, 43, 44). The pH value of this material increases after the mixing until 12,5. The high pH value allows the release of calcium ions and calcium hydroxide formation, and the antibacterial activity seems to be due to this fact (43, 45, 46). The biocompatibility, biomineralization and stimulation of cell differentiation are some positive biological properties of this material (43). However, discoloration after use, difficulty in the handling and mixing, and high cost are some of the recognized disadvantages of this material (43).

Animal and human studies showed a high success when MTA was used for VPT and the scientific evidence for its use is nowadays stronger than for any other material for this purpose (24, 47, 48).

Recently, new bioceramic materials were introduced, such as Biodentine™ (Septodont, Saint-Maur-des-Fosses, France) and Calcium Enriched Mixture (CEM) (BioniqueDent, Tehran, Iran) (24).

The Biodentine™ (Septodont, Saint-Maur-des-Fosses, France) is a bioceramic material that contains tricalcium silicate, calcium carbonate, zirconium oxide and calcium chloride. The zirconium oxide is the radiopaque agent. It is presented in a pre-dosage capsule: powder and the liquid are mixed in an equipment for this purpose. It is a biocompatible and non-cytotoxic material, compared with MTA there is no significant differences with cell viability (43). Compared to MTA, its properties were improved: easier mixing and handling, shorter initial setting time (43, 45) and less coronal discoloration (43, 49, 50).

The Calcium Enriched Mixture (CEM), also known as new endodontic cement, contains calcium oxide, sulfur trioxide, phosphorous pentoxide, silicon dioxide as major components. As minor components, it contains aluminium trioxide, sodium oxide, magnesium oxide and chloride (51).

When CEM is mixed with water-based solution, bioactive calcium and phosphate enriched mixture is formed. Calcium and phosphate ions are released and thereafter induce formation of hydroxyapatite (51). Its physical properties are almost similar to MTA. As biological properties, this bioceramic material has antibacterial and antifungal properties (inhibit *Candida Albicans* growth), is biocompatible, it releases calcium ions during setting and forms

hydroxyapatite crystals, induces hard tissue formation (particularly cementogenesis), and has a favorable cell viability (51).

These bioceramic materials have been suggested by different studies to perform appropriately when used in pulpotomy treatments (10, 11, 13, 16, 21, 24, 31, 32, 52-56).

AIM

Based on previous referred subjects, the aim of this study is to review the treatment outcome of posterior definitive mature teeth with irreversible pulpitis submitted to pulpotomy as an alternative to Conventional Endodontic treatment.

MATERIALS AND METHODS

This systematic review was performed following the PRISMA guidelines. The strategy search was conducted independently by 2 reviewers (JMS and JP) as shown in flowchart (Figure 1) and in Tables I and II via PubMed and EMBASE databases, respectively.

Search strategy was built by the following criteria:

Population: Posterior mature permanent teeth diagnosed with irreversible pulpitis.

Intervention: Total or Partial Pulpotomy.

Comparison: Root Canal Therapy.

Outcome: Clinical and radiographic success.

After these criteria, PICO question was formulated: “Could posterior mature permanent teeth diagnosed with irreversible pulpitis treated by pulpotomy (total or partial) expect an outcome (clinical and radiographic) similar to conventional endodontic treatment (pulpectomy)?”.

Relevant key words to the research topic were used. The search was limited to articles published between 2000 and 2018 (Pubmed/Medline: 2000-01-01 to 2018-05-31; Embase: 2000-2018 AND 2000-01-01 to 2018-05-31).

The articles that met the inclusion criteria were qualified for final selection.

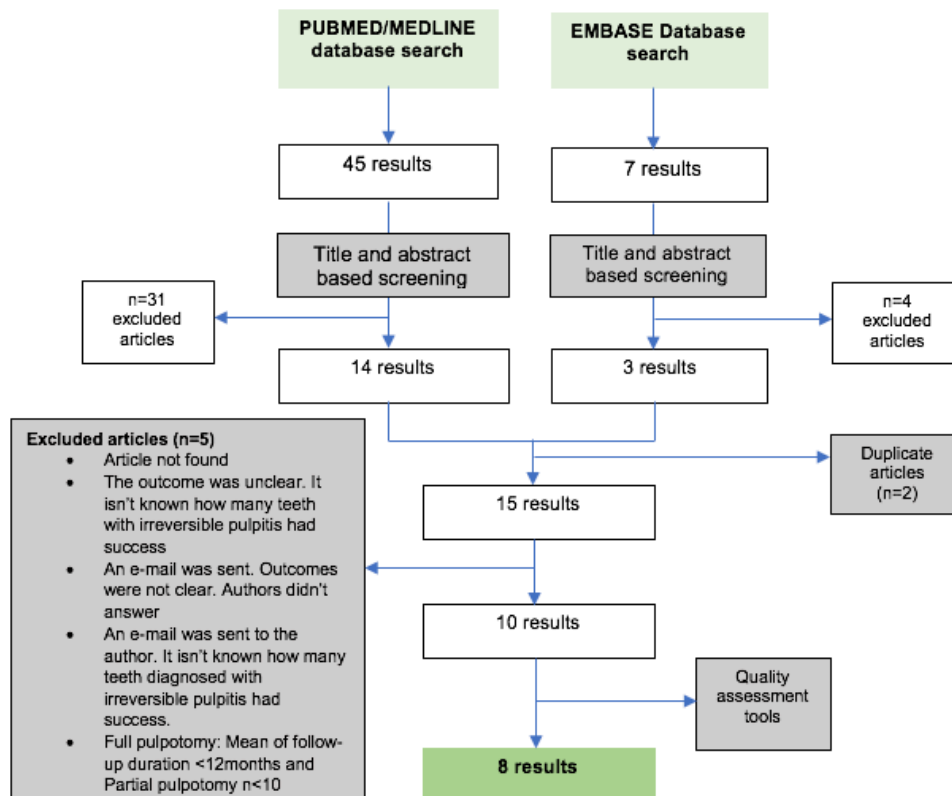


Figure 1- Flowchart of Methodology of search strategy for systematic review

Table I- Search Strategy on PUBMED/Medline database. MESH terms are represented in Capital letters.

PUBMED SEARCH STRATEGY	RESULTS
1. Irreversible	36714
2. PULPITIS	2597
3. Pulpitis	3122
4. Pulpotomy	1713
5. PULPOTOMY	1432
6. 1 AND 3	506
7. 6 OR 4	2170
8. 6 AND 4	49
9. 8 AND ("2000/01/01"[PDAT] : "2018/05/31"[PDAT])	45

Table II-Search Strategy on EMBASE database.

EMBASE SEARCH STRATEGY	RESULTS
1. Irreversible	75590
2. Pulpitis	3206
3. Pulpotomy	873
4. Vital Pulp Therapy	176
5. 1 AND 2	410
6. 5 AND 3	24
7. 4 AND 5	8
8. 7 AND [1-1-2000]/sd NOT [1-6-2018]/sd AND [2000-2018]/py	7

Data extraction and analysis

After the authors screened the titles and abstracts independently, articles were selected for full text reading. The selected articles to full reading between the reviewers were the same. Searching strategy was systematized in tables I and II.

Data was extracted by two authors independently to a specific data form created with this goal. The primary outcomes of interest for this review were clinical and radiographic success. Success was defined as absence of clinical signs (as sinus tract or edema) and symptoms (like pain, tenderness to percussion or palpation) associated with normal radiographic periapical tissues. The success rate was determined for each included study based on the number of successfully treated divided by the total number of cases. The recall rate for each individual study was also calculated.

Quality assessment

Two quality assessment tools were used based on study design of included studies. Cochrane risk of bias to Randomized Clinical Trials (Supplementary table I- Supplementary information) and ROBIS-I to non-randomized studies (Cohort studies and case series) (Supplementary table II- Supplementary information). The assessments were performed independently by two examiners (JMS, JP). Furthermore, the level of evidence of the studies was attributed based on Oxford Centre of Evidence Based Medicine.

RESULTS

Selected studies

As result of electronic search via PubMed/Medline and EMBASE databases, 52 studies were identified, 3 of 52 were duplicated. The title and abstract of all papers was screened by 2 reviewers (JMS, JP), to eliminate articles which clearly did not meet inclusion criteria (Table III). Reasons of exclusion of each database were represented in tables IV and V. 2 articles were duplicated and 15 articles were selected for full reading. There was agreement on the selected articles by the 2 reviewers.

After full reading, based on inclusion and exclusion criteria (table III) 5 articles were excluded (reasons of excluding the articles are presented in table VI) and 10 articles were included to this study (presented in table VII). After quality assessment, included studies with “low risk of bias” were ranked by study design: Randomized Clinical Trials (RCT) comparing pulpotomy with pulpectomy, RCT’s comparing different capping materials, prospective cohort studies and case series.

Table III- Inclusion and exclusion criteria

Inclusion Criteria	Exclusion Criteria
<ul style="list-style-type: none"> ▪ Human studies ▪ Pulpotomy in mature permanent human teeth with irreversible pulpitis ▪ Radiographic and Clinical Outcomes available ▪ Pulpotomy in posterior teeth (Premolars and molars) ▪ Absence of resorption and calcification ▪ Signs and symptoms of irreversible pulpitis ▪ More than or 1 year follow up ▪ Abstract available ▪ Clinical Trials ▪ Clinical Prospective studies ▪ Clinical Retrospective studies ▪ Final restoration ▪ Articles in English language 	<ul style="list-style-type: none"> ▪ Only Clinical or Radiographic Outcome available ▪ Animal studies available ▪ <i>In vitro</i> studies ▪ Immature permanent teeth ▪ Primary teeth ▪ Histologic study ▪ Carious exposure without signs and symptoms of irreversible pulpitis ▪ Presence of resorption or calcifications ▪ Anterior teeth ▪ Case Series n<10 ▪ Abstract non available ▪ Retracted article ▪ Repeated article ▪ Intermediate restorative material ▪ Narrative Review article ▪ Article not found ▪ Survival outcome

Table IV- Excluded Studies- title and abstract screening- PubMed/Medline Database

Articles (Authors and Year)	Cause of exclusion
Eren <i>et al</i> , 2018 Kérourédan <i>et al</i> , 2017 Brignardello-Petersen, 2017 Bane <i>et al</i> , 2016 Asgary & Eghbal, 2010 Nyerere <i>et al</i> , 2006	Clinical Outcome
Asgary <i>et al</i> , 2017 Ashraf,H <i>et al</i> , 2017 Soni, 2016 Asgary <i>et al</i> , 2016 Asgary & Kemal, 2015 Solomon <i>et al</i> , 2015 Asgary, 2011	Case Report
Sabbagh <i>et al</i> ,2016 Peng <i>et al</i> , 2015 Harandi <i>et al</i> , 2013	Immature permanent teeth
Memarpour <i>et al</i> , 2016 Parisay <i>et al</i> , 2015 Whaterhouse <i>et al</i> 2002	Primary teeth
Mousavi <i>et al</i> , 2016 Mente <i>et al</i> , 2016 Chueh & Chiang, 2010 Eghbal <i>et al</i> , 2009	Histologic study
Jalali <i>et al</i> , 2015 Dunlop <i>et al</i> , 2013 Elsharraww & Elbaghdady, 2007	Unrelated to the topic
Simon <i>et al</i> , 2013	No signs of irreversible pulpitis
Orhan <i>et al</i> , 2010	Indirect pulp therapy
Asgary & Eghbal, 2010	Retracted article
McDougal <i>et al</i> , 2004	Intermediate restoration
Yazdani <i>et al</i> , 2014	Health technology assessment

Table V- Excluded articles - EMBASE Database

Articles (Authors and Year)	Cause of exclusion
Zanini <i>et al</i> , 2017 (57) Rechenberg, <i>et al</i> 2016 (58)	Inflammatory mediators
Lin & Rosenberg, 2011 (59)	Unrelated to the topic
Whaterhouse <i>et al</i> 2002 (60)	Primary molars

Table VI- Excluded articles after full reading

Article (Authors and Year)	Cause of exclusion
Asgary <i>et al</i> , 2017 (61)	Not found (is not available for free)
Asgary <i>et al</i> , 2018 (21)	An e-mail was sent to the authors because follow up was unclear. They didn't answer.
Linsuwanont <i>et al</i> , 2017 (62)	It isn't known how many teeth diagnosed with irreversible pulpitis had success.
Asgary <i>et al</i> , 2014 (52)	Full pulpotomy: Mean of follow-up duration <12months and Partial pulpotomy n<10
Taha <i>et al</i> ,2017 (32)	An e-mail was sent to the authors. I It isn't known how many teeth diagnosed with irreversible pulpitis had success.

Table VII- Included studies

Author(s), Year	Journal	Article Title	Study design
Asgary& Ehsani, 2009 (63)	JCD	Permanent Molar pulpotomy with a new endodontic cement: A case series	Case Series
Asgary <i>et al</i> , 2012 (9)	Clin Oral Invest	One-year results of vital pulp therapy in permanent molars with irreversible pulpitis: an ongoing multicenter; randomized, non-inferiority clinical trial	RCT
Asgary <i>et al</i> , 2013 (10)	Clin Oral Invest	Two-year results of vital pulp therapy in permanent molars with irreversible pulpitis: an ongoing multicenter randomized clinical trial	RCT
Asgary & Eghbal, 2013 (12)	Acta Odontol Scand	Treatment outcomes of pulpotomy in permanent molars with irreversible pulpitis using biomaterials: a multi-center randomized controlled trial	RCT
Asgary <i>et al</i> , 2014 (11)	Clin Oral Invest	Five-Year results of vital pulp therapy in permanent molars with irreversible pulpitis: a non-inferiority multicenter randomized clinical trial	RCT
Kumar <i>et al</i> , 2016 (64)	Contemp. Clin Dent	Comparative evaluation of platelet-rich fibrin, mineral trioxide aggregate, and calcium hydroxide as pulpotomy agents in permanent molars with irreversible pulpitis: A randomized controlled trial	RCT
Qudeimat <i>et al</i> , 2017 (30)	Inter Endod J	Mineral trioxide aggregate pulpotomy for permanent molars with clinical signs indicative of irreversible pulpitis: a preliminary study	Prospective Cohort study
Taha & Khazali, 2017 (13)	J Endod	Partial Pulpotomy in Mature Permanent Teeth with Clinical Signs Indicative of Irreversible Pulpitis: A Randomized Clinical Trial	RCT
Taha & Abdelkhader, 2018 (16)	J Endod	Full pulpotomy with Biodentine in Symptomatic Young Permanent Teeth with Carious Exposure	Prospective Cohort Study
Taha & Abdelkhader, 2018 (31)	Inter Endod J	Outcome of full pulpotomy using Biodentine in adult patients with symptoms indicative of irreversible pulpitis	Prospective Cohort Study

Quality assessment of selected studies

Despite two articles included immature permanent molars (16, 30), only the mature permanent teeth treated in these studies were analyzed.

Only 5 RCTs selected had “low risk of bias”, this classification resulted from the evaluation items of the Cochrane assessment risk of bias tool (Supplementary Table I- Supplementary information).

In randomized clinical trials risk of bias tool, parameters classified as “uncertain” had different reasons: the clinical diagnosis was not clearly defined or confirmed (9-11) and blinding of participants and personnel was not described (12).

In Taha 2017 study (13) the blinding of participants and the professionals was not possible because the physical appearance of the different materials (it is easy to know which one is applied), consequently was attributed “high risk” to this criterion.

Only a RCT study (64) had an overall “high risk of bias” and it was excluded: the blinding of participants and personnel could not have been achieved, the description of randomization was not in agreement with the flow of the treatment protocol described (PRF procedure started before the beginning of pulpotomy treatment, therefore is not consistent with blinding) and calibration of radiographic evaluators is not described.

In non-randomized studies, risk of bias was assessed by ROBIS-I tool (Supplementary Table II- Supplementary information). Only a case series study (63) had an overall bias classified as “high”: selected participants were treated in a private clinic; inclusion criteria were very summarized; and clinical diagnosis wasn't clearly described (it was not referred the use of thermic or electrical tests to confirm irreversible pulpitis). The radiographic outcome measure was not described and calibration were also not referred. In general, is a poor study, as such was attributed overall high risk of bias.

The RCTs and non-randomized studies (case series excluded, only cohort studies included) finally included in this review had “low risk” in overall bias, its evaluation of bias items was described in supplementary tables I and II in supplementary information.

After this procedure and study design rank (RCT's comparing pulpotomy with pulpectomy, RCT's comparing different pulpotomy capping material's and prospective cohort studies) studies were evaluated: sample size, age range, material and type of procedure (total or partial pulpotomy), follow-up and success rate, recall rate and level of evidence (tables VIII, IX, X).

The majority of studies were ranked as level 1b in the evidence level of CEBM: the recall rate of each study is higher than 80%(9, 10, 12, 13, 16, 30, 31). The only study ranked as level 2b had recall rate lower than 80% (66,6%)(11).

Success rate analysis

As above referred, the studies were reported in tables VIII, IX and X associated by study design. It represented the age range of the study population, sample size, pulpotomy type, pulpotomy material, follow-up and success rate.

The success rate of pulpotomy procedure was calculated if the study reported the number of failed or success cases at the specific follow-up period or it was available in study report.

Only 3 studies compared pulpotomy with CET: at 1-year follow-up, clinical outcome is similar between both procedures (pulpotomy-97,6%; pulpectomy-98,3%), but radiographic outcome is better in pulpotomized teeth (9-11).

Overall, for 1 year follow-up five studies were available in this review (three randomized clinical trials and two prospective studies). In these studies, pulpotomies were performed with bioceramic materials and evidence a high success rate (table XI): clinical success rate ranges from 83% to 100% and radiographic success rate span between 83% to 98,4% (9, 12, 13, 16, 31).

At 2 years follow-up, two studies reported bioceramic pulpotomy's outcome, maintaining a high level of success rate, above 85% (10, 13).

One included study performed partial pulpotomy with calcium hydroxide (13) and showed the lowest success rate (55% at 1 year and 45% at 2 years follow-up) of all included studies, which deserves particular attention, because either the material (calcium hydroxide) or the pulpotomy technique (partial) were different from all other included studies (9-12, 16, 30, 31). Nevertheless, the partial pulpotomy study arm treated with ProRoot MTA showed a fair success rate at 2 years (85%), which is consistent with the results from studies performing full pulpotomy and supports the idea that results observed in this particular study were more influenced by the material than by the treatment technique (13).

A study was included in 60 months (11) follow-up and another study was included with a mean follow-up of 54,3 months (30): success rate was 78,1% and 100% respectively.

Recall rate was calculated based on number of patients who were available to recall evaluation in each specific follow-up period.

Table VIII-Included RCT's which compares Pulpotomy with pulpectomy

AUTHOR, YEAR	N	AGE RANGE	TYPE OF TEETH	PULPOTOMY PROCEDURE AND MATERIAL	1 YEAR F.UP	1 YEAR F.UP	2 YEARS F.UP	2 YEARS F.UP	MORE THAN 2 YEAR FOLLOW-UP CLINICAL SUCCESS RATE	MORE THAN 2 YEAR FOLLOW-UP RADIOGRAPHIC SUCCESS RATE	RECALL RATE	LOE 2009
					CLINICAL SUCCESS RATE	RADIOGRAPHIC SUCCESS RATE	CLINICAL SUCCESS RATE	RADIOGRAPHIC SUCCESS RATE				
Asgary et al, 2013 (9)	CEM n=205	6-65	Molars	Total Pulpotomy CEM	97,6%	92,2%	-	-	-	-	84%	1b
	2study arms CET n=202			CET	98,3%	70,3%	-	-	-	-		
Asgary et al, 2013 (10)	CEM n=166	6-65	Molars	Total Pulpotomy CEM	-	-	98.19%	86.1%	-	-	81,6%	1b
	2 study arms CET n=166			CET	-	-	98,19%	79,5%	-	-		
Asgary et al, 2014 (11)	CEM n=137	6-65	Molars	Total Pulpotomy CEM	-	-	-	-	60m= 78,1%		66,6%	2b
	2study arms CET N=134			CET	-	-	-	-	60m= 75,3%			

Table IX- Included RCT's which compares different materials in pulpotomy procedure

AUTHOR, YEAR	N	AGE RANGE	TYPE OF TEETH	PULPOTOMY PROCEDURE AND MATERIAL	1 YEAR F.UP	1 YEAR F.UP	2 YEARS F.UP	2 YEARS F.UP	MORE THAN 2 YEAR FOLLOW-UP CLINICAL SUCCESS RATE	MORE THAN 2 YEAR FOLLOW-UP RADIOGRAPHIC SUCCESS RATE	RECALL RATE	LOE 2009
					CLINICAL SUCCESS RATE	RADIOGRAPHIC SUCCESS RATE	CLINICAL SUCCESS RATE	RADIOGRAPHIC SUCCESS RATE				
Asgary & Eghbal, 2013 (12)	MTA n=208	26±9	Molars	Total Pulpotomy MTA	98,3%	95%	-	-	-	-	84%	1b
	2 study arms CEM n=205	27±8		Total Pulpotomy CEM	97,6%	92,8%	-	-	-	-		
Taha & Khazali, 2017 (13)	n=50	20-50	Molars	Partial Pulpotomy White Root MTA		83%		85%	-	-	98,1%	1b
				2study arms	Partial Pulpotomy CH		55%		43%	-		

Table X- Included Cohort Prospective studies

AUTHOR, YEAR	N	AGE RANGE	TYPE OF TEETH	PULPOTOMY PROCEDURE AND MATERIAL	1 YEAR F.UP	1 YEAR F.UP	2 YEARS F.UP	2 YEARS F.UP	MORE THAN 2 YEAR FOLLOW-UP CLINICAL SUCCESS RATE	MORE THAN 2 YEAR FOLLOW-UP RADIOGRAPHIC SUCCESS RATE	RECALL RATE	LOE 2009
					CLINICAL SUCCESS RATE	RADIOGRAPHIC SUCCESS RATE	CLINICAL SUCCESS RATE	RADIOGRAPHIC SUCCESS RATE				
Qudeimat et al, 2016 (30)	n=13	26±9	Molars	Total Pulpotomy MTA Grey MTA White	-	-	-	-	Mean 54,3m 100%	Mean 54,3m 100%	At least 92,8%	1b
Taha & Abdulkhader, 2018 (16)	n=17	9-17	Molars	Total Pulpotomy Biodentine™	100%	94,1%	-	-	-	-	100%	1b
Taha & Abdulkhader, 2018 (31)	n=64	19-69	Molars	Total Pulpotomy Biodentine™	100%	98,4%	-	-	-	-	98,4%	1b

Table XI- 1 year Follow-up studies performed with bioceramic materials

Study Design	Study (Author, Year)	Material	Clinical Success Rate	Radiographic Success Rate
RCT	Asgary. et al, 2013	MTA	98,3%	95%
		CEM	97,6%	92,8%
	Asgary et al, 2013	CEM	97,6%	92,2%
	Taha & Khazali , 2017	MTA	83%	83%
CH		55%	55%	
Prospective Studies	Taha & Abdelkhader, 2018	Biodentine™	100%	98,4%
	Taha & Abdelkhader, 2018	Biodentine™	100%	94,1%

DISCUSSION

Excluding the partial pulpotomy with calcium hydroxide, all the studies with 1-year follow-up included in this review showed a success rate higher than 80%. Although we did not perform meta-analysis of the results, the clinical success is high (mean 90%) as well as the radiographic success also is high (mean 87%).

There are also 2-year follow-up studies, performed with bioceramic materials, which revealed high success rate, ranging from 85% to 98,19%. At 2-years follow-up pulpotomy treatment in mature teeth revealed similar results to previous reports in immature permanent teeth (14), rejecting the poor possibility of older pulps heal (26).

In the majority of studies (which separate clinical success from radiographic success)(9, 10, 12, 16, 30, 31) the clinical success rate is higher than radiographic success. This fact can be related with dependence on patients' symptomatology in clinical success, whereas radiographic success depends on evaluation of periapical bone with restricted criteria. Clinical success isn't a synonymous of radiographic success: symptomatology may be absent and clinically teeth may be normal with presence of radiographical periapical changes.

Two types of pulpotomy technique were performed in included studies: total (9-12, 16, 30, 31) and partial (13). Partial pulpotomy compared with total pulpotomy showed lower success rate (ranges 83-85%). The use of total pulpotomy is more predictable in removing inflamed tissue (14) , despite of this fact, both techniques in included studies had success rate higher or equal than 83%.

It is important to refer that there are few clinical studies which evaluate VPT in mature permanent teeth with signs and symptoms of irreversible pulpitis and only three authors' groups developed clinical researches for this purpose. Meta-analysis of these studies is premature because of the outcome and inclusion criteria difference between the studies, would bias the interpretation of the resulted mean success rate and negative effects could appear (38). Before including pulpotomy as an endodontic alternative treatment is important consider the validation of pulpotomy's indications and their pertinent outcome criteria. In general, the studies which evaluate this procedure, include different inclusion criteria and outcome criteria which could bias the results' interpretation. High success rate of the procedure allows interpretation of pulpotomy as an easy technique, but different factors need to be evaluated (38) and reports from different geographical and background dentistry formation need to became available, before we clearly address indications for the use of pulpotomy. The success of pulpotomy technique depends on several factors, such as bleeding time control, anesthetics

used (23), procedure, disinfection field materials, capping materials, permanent restoration, among other factors (9-12).

Contrary to Wolters *et al* 2017 study, there is limitations with studies which compare CET with Pulpotomy. Although only three included studies compared them (9-11), the high success rate of pulpotomy in the majority of the studies, may be suggest pulpotomy as an alternative treatment to teeth diagnosed with irreversible pulpitis. Histologic studies, both with teeth with or without signs of irreversible pulpitis showed high success rate after pulpotomy (29, 56). A dentinal bridge of reparative dentin formed under the capping material and absence of inflamed pulp tissue were observed in a tooth with signs of irreversible pulpitis (29). Despite of the absence of inflammation, the pulp state after pulpotomy can evolve and irreversible pulpitis can occur 2 months post-operative (38).

More studies which compare CET with pulpotomy are necessary, with more restricted inclusion criteria and clarified diagnosis foundation, to understand the pulpotomy's indications.

According Zanini *et al*, studies should be designed following the accepted and approved terminology by AAE: all studies in this review designated irreversible pulpitis as a diagnosis.

To diagnose well the cases of irreversible pulpitis is not only needed the presence of a spontaneous pain as a symptom of this condition, but also needed to do clinical tests (thermal and electric) and clinically is necessary confirm the presence of bleeding.

According Taha and Abdelkader, although the teeth are previously considered as irreversibly inflamed, clinically 16 teeth were not bleeding (necrosis), pulp was partially necrotic or hemostasis was not achieved. This study is a reason to explain the need of diagnosis confirmation after health centers' references. In Asgary *et al* one-year (9), two-year (10) and five-year (11) follow-up studies, there was a lack of this information after health centers' recommendation.

The clinical success criteria were different between studies: the majority of studies focused on absence of symptomatology, but in some studies, probing depth, integrity of definitive restoration, discoloration and mobility were evaluated (13, 16, 30, 31).

In some included studies, "clinical success" is considered when cold test result is positive (13), but thermal and electric clinical tests to assess vitality is hard in pulpotomized teeth: the presence of a restoration and deposit of tertiary or reparative dentin could decrease the reliability of these clinical tests (38). Bearing in mind this, the efficacy of pulpotomy procedure is more related to the absence of signs of periapical inflammation than the presence of healthy radicular pulp tissue (38) and sometimes the presence of infection is used to assess pulp vitality indirectly. Moreover, being a clinical success does not mean to have presence of vital

pulp; the teeth may be asymptomatic and may not have a radiographic evidence of pathosis, however the pulp tissue may already be necrotic (4, 31).

Zanini *et al* referred that it is important to refer the sealing properties of restoration and probing depth in clinical outcomes, if they fail, microleakage is possible and the pulpotomy procedure can also fail (38). The significance of prevention of coronal microleakage to avoid endodontic treatment failure (apical periodontitis development) has been previously demonstrated with *in vivo* studies (65, 66).

In Taha's study, none of teeth presented with discoloration(31). This fact may be related with bioceramic material used, Biodentine™, which contains zirconium oxide as a radiopaque material and have proved to induce lower discoloration than classical MTA materials (24, 31, 45).

The aim of radiographic evaluation is comparing the periapical state during a period. This criterion to be reliable needs to be performed by calibrated evaluators and the studies need to refer and describe the procedure, to guarantee unbiased evaluation (38).

In all Asgary *et al* studies radiographic success was determined based on modified Strindberg criteria (9-12), while Taha's studies based on PAI (13, 16, 31). In both criteria is considered the periapical area healing: In score of PAI is reduced and in Strindberg criteria is classified as "healing".

Dentinal bridge under pulp capping material can be accepted as a radiographic criterion: none of the studies suggested the radiographic evidence of dentin bridge under material, as success criteria, according to Zanini *et al*, radiographic evidence of dentinal bridge is not reliable (low mineralization grade under the capping material, root overlap and restorative materials) (38). In Taha's study, 4 teeth evidenced presence of this bridge under the capping material (31). This criterion can be clinically evaluated, but there is a contamination risk (the capping material needs to be removed and dentinal bridge presence confirmed with a probe) and this procedure isn't recommended nowadays in follow-up studies (31, 38).

In general, "success" is the absence of pulp infection and can be reported as an absence of periapical inflammation or external resorption. Absence of periapical pathology is assumed when clinical tests are negative and periapical ligament enlargement or apical radiolucency are absent, but in pulpotomized teeth cases, absence of symptomatology is more reliable than the clinical tests (37, 38).

The bleeding time control is not established yet, in included studies minimum time is 2-3minutes and maximum is variable (a study referred if required, more 2-3minutes (13) and others referred repetition of compression up to 6 minutes (16, 31). There are some studies which didn't specify the time used for bleeding control. Local anesthetics used are different between

the studies, and vasoconstrictor concentration also varies (2% lidocaine with 1:80000 epinephrine (9-13, 16, 30) and 4% articaine with 1:100 000 epinephrine (31) and the composition of anesthetics would influence the intra-operative irreversible pulpitis diagnosis confirmation, vasoconstrictor compound could influence the bleeding. In Taha *et al* study , teeth with prolonged bleeding control time were associated with higher failure rate (3/7 failed) (32). If the pulp tissue under the capping material is inflamed the success rate may be influenced and the case may become a failure.

Before, it was believed that the apical radiolucency was a pathognomonic sign of necrosis. Today it is well described the simultaneous presence of periapical radiolucency and vital tissue, explained by the presence of bacterial products capable of inducing pulp inflammation and its extension to periapical tissues (16, 62, 67). In three included studies previous apical radiolucencies were reported: in Taha's study, 8 teeth with this condition were included (more 1 case but declined recall because of pregnancy) and 7 resolved after the procedure (31). In a posterior study, also included 7 teeth with apical radiolucencies, 5/7 completely healed and 2/7 reduced the periapical lesion size (16). Qudeimat *et al* also reported 7 teeth included with periapical pathology and all resolved at the end of the study follow-up (30). Other study, showed also, solved radiolucencies in 16/21 cases after pulpotomy (62).

Pulp biology knowledge development suggests that pulp response to release bioactive growth factors is related with regenerative capacities and inflammation is a part of normal pulp healing (8).

After the pulpotomy procedure the absence of pain is a clinical success criterion. Some studies reported reduction of pain index after this vital pulp therapy (19, 68), an option treatment to extraction to pain relief (12, 19) and significant differences in pain were not reported between this procedure and CET (20). Several previous studies suggested this treatment an option to teeth without signs of irreversible pulpitis (69) or with reversible pulpitis (53). The results of this review evidenced a favorable success rate of pulpotomy (partial or full) in treating painful teeth.

Although Biodentine™ had a higher success rate than MTA, both materials in pulpotomy treatment exhibited high success rates. The same did not happen with the calcium hydroxide. In histologic study, calcium hydroxide pulpotomies didn't present a complete calcified dentin bridge, in clinical studies bioceramic materials have shown better clinical outcome than calcium hydroxide. The improvement of endodontic materials provided a better option to vital pulp therapy procedures (30, 54).

According Taha and Abdelkader, is suggested indirect cusp coverage to all success teeth treated by pulpotomy procedure at 1year follow-up (31). This recommendation is based on

biomechanics: fractures are more frequent on endodontic treated teeth without reduction of cusps (70).

The recall rate of all included studies is higher than 80%, with only one study below this level (11). According to Friedman, at least 80% of recall rate is needed for a study to be considered as a high level of evidence (71). The only study that did not comply with this criterion for high level of evidence, presented the results with the longer follow-up, which justify the increased number of patients lost to follow-up (11).

CONCLUSION

This systematic review found high level of evidence which reports high success rate for pulpotomy. As clinical and radiographic success is similar to CET, this procedure seems to be a potential alternative approach to treat mature teeth with irreversible pulpitis.

However, It is important to refer that there are few clinical studies which compare both treatment approaches, pulpotomy with CET. Also, the majority of studies only presented 1-year follow-up (only a study reported a longer follow-up but the recall rate and evidence level were the lowest) and only three authors' groups developed clinical researches for this purpose.

The actual evidence of the included studies of this systematic review suggests that is ethical and correct to design further studies to compare both alternatives. This development is needed to clarify the appropriate clinical conditions to apply this technique with predictable results and strength the evidence for using pulpotomy. Furthermore, there's a demand for studies with longer follow-up periods, reasonably with 4 years, to allow a truly comparison with the expected outcome for conventional endodontic treatment of teeth presenting with this clinical diagnosis.

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SUPPLEMENTARY INFORMATION

Supplementary table I- Risk of bias to RCT studies- based on Cochrane Collaboration tool

	<i>Asgary et al, 2013</i>	<i>Asgary et al 2014</i>	<i>Asgary et al 2015</i>	<i>Asgary & Eghbal, 2013</i>	<i>Taha & Khazali, 2017</i>	<i>Kumar et al, 2016</i>
1.RANDOM SEQUENCE GENERATION	LOW	LOW	LOW	LOW	LOW	LOW
2.ALLOCATION CONCEALMENT	LOW	LOW	LOW	LOW	LOW	LOW
3. BLINDING OF PARTICIPANTS AND PERSONNEL	LOW	LOW	LOW	UNCERTAIN	HIGH	HIGH
4. BLINDING OF OUTCOME ASSESSMENT	LOW	LOW	LOW	LOW	LOW	LOW
5.INCOMPLETE OUTCOME DATA	LOW	LOW	LOW	LOW	LOW	LOW
6.SELECTIVE REPORTING	LOW	LOW	LOW	LOW	LOW	LOW
7.OTHER SOURCES OF BIAS	UNCERTAIN	UNCERTAIN	UNCERTAIN	LOW	LOW	HIGH
8. FINAL RISK OF BIAS	LOW	LOW	LOW	LOW	FAIR	HIGH

Supplementary table II- Risk of bias to non-randomized studies based on ROBIS-I tool

	<i>Qudeimat et al, 2017</i>	<i>Taha & Abdelkader, 2018</i>	<i>Taha & Abdelkader, 2018</i>	<i>Asgary,S. & Ehsani,S.,2009</i>
1.BIAS DUE TO CONFOUNDING	LOW	LOW	LOW	LOW
2.BIAS IN SELECTION OF PARTICIPANTS INTO THE STUDY	LOW	LOW	LOW	SERIOUS
3.BIAS IN CLASSIFICATION OF INTERVENTIONS	LOW	LOW	LOW	LOW
4.BIAS DUE TO DEVIATIONS FROM INTENDED INTERVENTIONS	LOW	LOW	LOW	N/A
5.BIAS DUE TO MISSING DATA	LOW	LOW	LOW	LOW
6.BIAS IN MEASUREMENT OF OUTCOMES	LOW	LOW	LOW	SERIOUS
7.BIAS IN SELECTION OF THE REPORTED RESULT	LOW	LOW	LOW	N/A
OVERALL BIAS	LOW	LOW	LOW	HIGH

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