INSTITUTO UNIVERSITÁRIO EGAS MONIZ

MESTRADO INTEGRADO EM MEDICINA DENTÁRIA

CLINICAL EVIDENCE OF VITAL PULP THERAPY IN CARIOUSLY EXPOSED PERMANENT MATURE TEETH SYSTEMATIC REVIEW AND META-ANALYSIS

Trabalho submetido por
Eduardo Soares Penques
para a obtenção do grau de Mestre em Medicina Dentária

setembro de 2021

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RESUMO

Introdução: O tratamento de dentes pode ser efectuado recorrendo a diferentes terapias de polpa vital (proteção pulpar direta, pulpotomia parcial e pulpotomia total) as quais se encontram reportadas, na literatura, como opções viáveis dado apresentarem elevada taxa de sucesso a curto prazo.

Metodologia: Foi realizada uma pesquisa bibliográfica entre 01/01/2011 e 03/10/2021, nas bases de dados do PubMed, B-on, Scopus e Web of Science, seguindo o protocolo de busca registrado na PROSPERO sob o nº CRD42021256409, tendo como base a seguinte questão de investigação: "Qual a eficácia relativa dos protocolos de terapia de polpa vital utilizados para tratar dentes com envolvimento pulpar?" foi realizada análise de risco de viés com a ferramenta RoB2. A meta-análise sintetizou inicialmente apenas a evidência proveniente de comparações diretas através da plataforma RevMan web, utilizando modelos para efeitos randomizados. Foi posteriormente realizada uma meta-análise em rede, usando o software Stata 17, para sintetizar a evidência disponível, integrando as estimativas directas e indirectas.

Resultados: Foram incluídos dezasseis estudos na presente revisão, após aplicação dos critérios de inclusão aos resultados da pesquisa. Após avaliação de risco de enviesamento e processamento de dados com ferramentas de meta-análise, os dados mostraram que o tratamento de pulpotomia total com Biodentine™ é provavelmente a melhor opção de tratamento na terapia pulpar vital, seguido de pulpotomia parcial com MTA e capeamento pulpar direto com MTA e pulpotomia total com MTA.

Conclusão: Os tratamentos da polpa vital são uma opção de tratamento interessante que permite a manutenção da vitalidade pulpar associada a bons resultados a longo prazo. Os novos biomateriais têm se mostrado superiores aos tratamentos já estabelecidos, com o MTA apresentando bons resultados tanto na proteção pulpar directa quanto na pulpotomia parcial e total, com o Biodentine™ apresentando-se como o melhor resultado, mas apenas na pulpotomia total.

Palavras-Chave: Terapia de polpa vital, MTA, Biodentine™, Hidróxido de cálcio.

ABSTRACT

Introduction: The treatment of teeth can be carried out using different vital pulp therapies (direct pulp capping, partial pulpotomy and total pulpotomy) which are reported in the literature as viable options given their high short-term success rate.

Methodology: A bibliographic search was carried out between 01/01/2011 and 10/03/2021, in the databases of PubMed, B-on, Scopus and Web of Science, following the search protocol registered in PROSPERO under number CRD42021256409, having as based on the following research question: "What is the relative effectiveness of vital pulp therapy protocols used to treat teeth with pulp involvement?" risk of bias analysis was performed with the RoB2 tool. The meta-analysis initially synthesized only evidence from direct comparisons through the RevMan web platform, using models for randomized effects. A network meta-analysis was then performed, using Stata 17 software, to synthesize the available evidence, integrating direct and indirect estimates.

Results: Sixteen studies were included in this review, after applying the inclusion criteria to the research results. After risk assessment of bias and data processing with meta-analysis tools, the data showed that the treatment of total pulpotomy with biodentin is probably the best treatment option in vital pulp therapy, followed by partial pulpotomy with MTA and direct pulp capping with MTA and total pulpotomy with MTA.

Conclusion: Vital pulp treatments are an interesting treatment option that allows the maintenance of pulp vitality associated with good long-term results. The new biomaterials have proven to be superior to established treatments, with MTA presenting good results both in direct pulp capping and in partial and total pulpotomy, with biodentin presenting itself as the best result, but only in total pulpotomy.

Keywords: Vital Pulp Therapy, MTA, Biodentine™, Calcium Hydroxide.

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(partial pulpotomy using Biodentine™); **PP_CEM** (partial pulpotomy using material based on calcium silicate); **PP_CH** (partial pulpotomy using calcium hydroxide); **PP_MTA** (partial pulpotomy using mineral trioxide aggregate); **RCT** (root canal treatment). 32

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LIST OF ABREVIATIONS

CEM	Calcium enriched mixture cement
DPC	Direct pulp capping
FP	Full pulpotomy
IUEM	Instituto Universitário Egas Moniz
MTA	Mineral trioxide aggregate
PP	Partial pulpotomy
WPS	Weighted pooled success rate
CI	Confidence interval
LOE	Level of evidence
ns	Number of successful
nt	**N**umber of total sample
DPC_Biodentine™	Direct pulp capping using Biodentine™
DPC_CEM	Direct pulp capping using material based on calcium silicate
DPC_CH	Direct pulp capping using calcium hydroxide
DPC_MTA	Direct pulp capping using mineral trioxide aggregate
FP_Biodentine™	Full pulpotomy using Biodentine™
FP_CEM	Full pulpotomy using material based on calcium silicate
FP_CH	Full pulpotomy using calcium hydroxide
FP_MTA	Direct full pulpotomy using mineral trioxide aggregate
PP_Biodentine™	Partial pulpotomy using Biodentine™
PP_CEM	Partial pulpotomy using material based on calcium silicate
PP_CH	Partial pulpotomy using calcium hydroxide
PP_MTA	Partial pulpotomy using mineral trioxide aggregate
RCT	Root canal treatment

I. INTRODUCTION

The treatment of vital teeth with extensive caries lesions with pulp involvement is quite controversial with several treatment options available and accepted as viable to treat these teeth (Didilescu et al., 2018; Schwendicke et al., 2015; Taha et al., 2020). Vital pulp therapy option (a procedure described by Pfaff in 1756) offers minimal intervention, by covering the exposed pulp with a lead sheet cover in order to preserve the tooth structure and prevent damage to the dentin-pulp complex (Chen et al., 2019; Mente et al., 2014; Taha et al., 2020; Vural et al., 2017). The literature success rates reported, of this procedure, are however inconsistent (varying between 37% to 100%) (Bogen et al., 2008; da Rosa et al., 2019; Mente et al., 2014; Miyashita et al., 2016; Schwendicke et al., 2015; Vural et al., 2017) and are associated with an exacerbation of postoperative pain when the proposed treatment fails, leading to a worsening of the patient's clinical condition (Didilescu et al., 2018; Mathur et al., 2016).

The treatment of vital pulp therapy is dependent of determination pulp condition. Several tests have been used to determine the pulp health status, the most used and accepted test is the pulp vitality test (cold or heat test), (Didilescu et al., 2018; Gudkina et al., 2012; Nair et al., 2008; Qudeimat et al., 2007). These tests show results that are derived from the patient's painful experience, which can lead to a misdiagnosis in relation to the histological examination, where the pulp condition is determined by the inflammatory condition of the tissues, with the presence of mild inflammation being considered reversible pulpitis (Mente et al., 2014; Miyashita et al., 2016; Vural et al., 2017), however there is still a lack of a precise approach to diagnose the condition of the pulp (Gudkina et al., 2012; Taha et al., 2020).

Besides vital pulp therapy or other therapy options were explored, such as, direct pulp capping, partial pulpotomy and total pulpotomy (Schwendicke et al., 2016). Vital pulp therapies are indicated for teeth that do not show periodontal or periapical involvement, that do not show pulp involvement with irreversible pulpitis and in teeth that show pulp exposure caused by mechanical action during removal of carious tissue or trauma (Qudeimat et al., 2007; Schwendicke et al., 2016), however in several recent studies good results of vital pulp therapy were demonstrate, even in teeth that present with signs and symptoms of irreversible pulp alteration (Aguilar & Linsuwanont, 2011; Asgary et al., 2013, 2017, 2018; Linu et al., 2017; Malekafzali et al., 2011; Nair et al.,

2008; Parinyaprom et al., 2018; Parirokh et al., 2011; Parvin et al., 2018; Rada, 2013). Traditional endodontic treatment has been accepted as the most accepted treatment to prevent or treat the occurrence of apical periodontitis, however recent studies have shown that vital pulp therapy, especially partial or total pulpotomy, should be considered as a therapeutic option for patients with pulp involvement but without signs and symptoms of irreversible pulp change (Ward, 2002) (Aguilar & Linsuwanont, 2011). Other treatment proposals are described, such as, conservative treatments for teeth with pulp involvement, that aim to avoid endodontic treatment, revealed loss of propioceptive function, cushioning property and tooth sensitivity, since these mechanisms provide a defense against harmful stimuli, resulting in a worse prognosis in terms of survival than vital teeth (Alobaid et al., 2014; Didilescu et al., 2018; Fonzar et al., 2018; Schwendicke et al., 2016; Silveira et al., 2015).

Regarding the materials used for the conservative treatment of the pulp, the mixtures enriched with calcium (CEM) are the most used material for vital pulp therapy, namely direct pulp capping, partial pulpotomy and total pulpotomy (Aguilar & Linsuwanont, 2011; Asgary et al., 2017; Chen et al., 2019; da Rosa et al., 2019; Schwendicke et al., 2015, 2016), however, since the 1990s, mineral thioxide aggregate (MTA), revealed excellent results in terms of physical / chemical properties, antibacterial activity, biocompatibility, sealing properties and clinical success rates, and become the material of choice used on a daily basis in clinical practice (Aguilar & Linsuwanont, 2011; Bogen et al., 2008; Chen et al., 2019; Donovan et al., 2012; Mahmoud et al., 2018; Nair et al., 2008; Parinyaprom et al., 2018; Parvin et al., 2018; Qudeimat et al., 2007; Schwendicke et al., 2015; Shivashankar et al., 2017; Torabinejad & Turman, 2011).

With the evolution of dental materials, new materials have emerged, which have become popular due to their biological characteristics, physical-chemical qualities and especially their ability to induce a regeneration of dental hard tissues. Among these new materials MTA, Biodentine™ and CEM, become an excellent option for performing vital pulp therapy procedures and are easy to handle (Bogen et al., 2008; Chen et al., 2019; Mahmoud et al., 2018; Parvin et al., 2018; Schwendicke et al., 2016).

The development of treatment materials and techniques, in the last decades, offers a range of options with different outcomes reported in different studies that can make it difficult to choose the best clinical decision. This decision should be based on the best levels of evidence which can only be achieved by a focused and systematic literature

analysis which can be provided by systematic reviews and meta-analyzes (Aguilar & Linsuwanont, 2011; Chen et al., 2019; Cushley et al., 2021; da Rosa et al., 2019; Deng et al., 2016; Mahmoud et al., 2018; Munir et al., 2020; Schwendicke et al., 2015).

The main objective of this work was to carry out a systematic review of the literature on vital pulp therapy, followed by a network meta-analysis to seek to determine the best material (calcium hydroxide, MTA, Biodentine™ and CEM) and treatment option (direct pulp capping, partial pulpotomy and total pulpotomy) for teeth that can be treated with vital pulp therapy.

II. MATERIALS AND METHODS

This systematic review, was registered in PROSPERO under number CRD42021256409, and reported using the PRISMA-NMA statement and the PICO framework (P – patients with permanent teeth with pulp exposure, I - treatment with vital pulp therapy direct pulp caping, C – full pulpotomy and partial pulpotomy, O - Success rate of treatments, based on the following question: "What is the relative effectiveness of vital pulp therapy protocols used to treat teeth with pulp involvement?"

Information sources and search strategy

In order to obtain relevant studies to answer the question of this review, the following combination of words used in the search in the databases of PubMed, B-on, Scopus and Web of Science were used: (“Pulp Capping” AND “Vital Pulp Therapy” AND “Permanent”) OR (“Pulp Capping” AND “Permanent” AND “Mineral Trioxide Aggregate”) OR (“Vital Pulp Therapy” AND “Permanent” AND “Mineral Trioxide Aggregate”), by 2 independent reviewers (E.S.P., M.F.S.J.). From the search in the databases, articles published between 01/01/2011 and 03/10/2021 were considered for analysis.

Studies selection process

Inclusion Criteria

Studies that evaluated permanent teeth with pulp exposure and that presented a well-defined diagnosis without inclusion of teeth with irreversible pulpitis or doubtful pulp diagnosis, submitted to vital pulp therapy treatment (Direct pulp capping (DPC), partial pulpotomy (PP)) were included. and total pulpotomy (FP)) using calcium hydroxide (CH), Mineral Trioxide Aggregate (MTA), Biodentine™ or calcium-enriched

cement mixture (CEM) as pulp lining materials, which presented a minimum follow-up period of 12 months. The main outcome evaluated was the clinical and radiographic success rate after a 12-month period, characterized by the absence of signs and symptoms of pulp involvement, without the need for endodontic treatment or tooth extraction.

Exclusion Criteria

Studies that evaluated vital pulp therapy in primary teeth that did not present a clear pulp diagnosis or with the inclusion of teeth with a diagnosis of irreversible pulpitis were excluded. Case reports, review works, studies in animals or in vitro or studies that did not use at least two of the materials objects of evaluation of this study were also excluded.

Data collection/extraction process

Data extraction was performed independently by two reviewers (ESP, MFSJ). Data were extracted regarding study information (author and year), study designer, number of teeth included in the analysis, diagnosis of teeth included in the study, what intervention and what material was used in these teeth, the follow-up time and the number of teeth that were lost for follow-up, as well as the main results.

A table was also set up to be used in the construction of the database with data related to each of the treatments performed for the assembly of the network and comparison between treatments, these data were used to estimate the effect of the interventions through odds ratios (OR) with a 95% confidence interval (CI).

All data were extracted and analyzed considering the tooth treated as a unit and not the patient (e. g., in cases where two teeth were treated in the same patient, two interventions were considered in isolation).

Quality assessment – Risk of bias

The quality of the studies included in this review was analyzed using the RoB2 risk of bias analysis tool (Cochrane) (Higgins et al. 2016). Bias risk analysis was conducted independently by two reviewers (E.S.P., M.F.S.J.). During bias analysis the data were tabulated using a Microsoft Excel spreadsheet which was used to generate the bias analysis charts, the classification criteria for judging the risk of bias are described in table 1.

Table 1: General pattern for the assessment of the risk of bias.

Risk of bias	Interpretation	Within a study
Low risk of bias	Plausible bias unlikely to alter the results seriously	Low risk of bias for all key domains
Unclear risk of bias	A plausible bias that raises some doubt about the results	Unclear risk of bias for one or more key domains
High risk of bias	A plausible bias that seriously weakens confidence in the results	High risk of bias for one or more key domains

Data Synthesis and Analysis

Description of the available evidence

To organize the data, the treatments were grouped as follows:

DPC_Biodentine™ (direct pulp capping using Biodentine™);

DPC_CEM (direct pulp capping using material based on calcium silicate);

DPC_CH (direct pulp capping using calcium hydroxide);

DPC_MTA (direct pulp capping using mineral trioxide aggregate);

FP_Biodentine™ (full pulpotomy using Biodentine™);

FP_CEM (full pulpotomy using material based on calcium silicate);

FP_CH (full pulpotomy using calcium hydroxide);

FP_MTA (direct full pulpotomy using mineral trioxide aggregate);

PP_Biodentine™ (partial pulpotomy using Biodentine™);

PP_CEM (partial pulpotomy using material based on calcium silicate);

PP_CH (partial pulpotomy using calcium hydroxide);

PP_MTA (partial pulpotomy using mineral trioxide aggregate);

RCT (root canal treatment).

All characteristics of the included studies were considered and treatment protocols using vital pulp therapy for the individual studies reported.

The comparison of direct evidence between the different protocols analyzed in the individual studies was illustrated by means of the network diagram and all protocols not connected to the network diagram were excluded.

The methodology was analyzed using the technique of population, intervention, comparison and result (PICO) of the included studies to verify the presumption of similarity in the methodology used in the studies, an important assumption for the realization of the network. The transitivity assumption (studies that compare A and C have no relationship with B and that studies that compare A and B have no relationship with C, considering that the comparison B and C does not exist. Interpretively, we can state that if treatment B is hypothetically better than A and if A is better than C, then it can be assumed that B is better than C) was statistically evaluated using consistency tests.

Meta-analysis in direct comparison

In the presence of two or more studies with the same pair of treatment comparison (example: DPC_Biodentine™ vs. DPC_MTA) a meta-analysis was conducted, to estimate the direct effect between treatments and the associated heterogeneity. Meta-analysis was conducted in the RevMan network, using the random effects model with the effect's analysis performed by the Mantel-Haenszel method. The heterogeneity analysis was performed by test I^2, considering between 0 and 25% low heterogeneity, between 25% and 50% moderate heterogeneity and above 50% high heterogeneity. An empirical correction was made for studies that had a null effect in one of their intervals. Any study with an effect size of zero in both intervals was excluded.

Network meta-analysis (NMA)

The network meta-analysis was conducted with Stata 17 (StataCorp, CollegeStation, TX, USA), using the netowrk, mvmeta and netwoprk graphics package for interpretation and generation of network graphics.

For the formation of the network, it was considered that all included patients meeting the inclusion criteria had, in principle, the same probability of being in any of the arms of the included studies. The treatment protocols were grouped according to the type of intervention performed in: direct pulp capping (DPC) with (Biodentin, Calciun hydroxide, CEM and MTA), total pulpotomy (FP) with (Biodentin, Calciun hydroxide, CEM and MTA), partial pulpotomy (PP) with (Biodentin, Calciun hydroxide, CEM and MTA). Protocols were evaluated through the distribution of accumulated probabilities under the cumulative accumulation curves (SUCRA), in order to determine which treatment option was likely to be the most effective. Furthermore, the obtained pooled effects and associated uncertainty were graphically compared in a forest plot.

III. RESULTS

The initial search resulted in 2074 articles (figure 1). After removing duplicates using the Mendeley® citation manager, 1895 articles remained, which were analyzed by their title and abstract about their eligibility for this review. Thirty-one articles were selected for analysis of the entire text, 2 the full texts were not obtained, they were thus excluded, after the analysis of the complete text 13 studies were excluded according with the exclusion criteria described in Anexo 1.

Data on the success rate were calculated using the 12-month follow-up. Asgary study (S Asgary et al., 2014) was excluded from the quantitative analysis as it presented 24-month follow-up data for the same sample used in the study previous author study (Saeed Asgary et al. 2013), differing only in the follow-up time.

The remaining 16 studies were analyzed and included in the data analysis of this review, table 2 and figure 1.

The analysis of the success rate in vital pulp therapy included data from 16 RCTs reporting 340 (18.87%) failures in 1802 treated teeth, the data are summarized in annex 2.

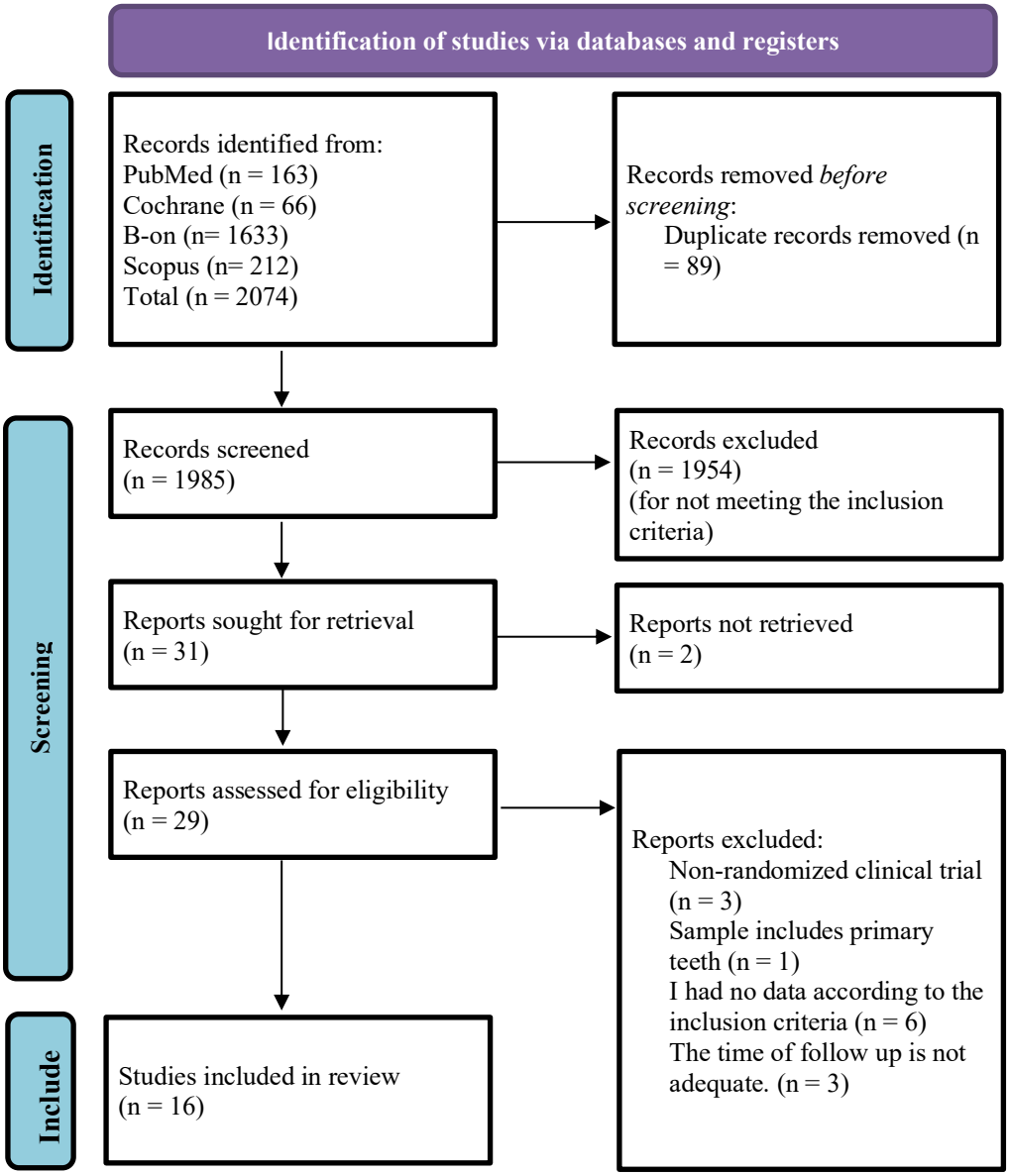

Figure 1: Flow chart of search strategy and number of included articles

Table 2: Main data from the studies included in the review

Study (Year)/ Location	Study Design	Number of teeth	Diagnosis	Intervention	Capping material	Follow-up (months)	Drop outs (lost patients)	OUTCOMES
(Abuelniel et al., 2020)/Egypt	RCT	50	crown fracture with pulp exposure	Full pulpotomy	Biodentine™ and MTA	12	4	Both MTA and Biodentine™ showed similar clinical and radiographic outcomes when used as pulpotomy materials in the treatment of traumatized immature anterior permanent teeth. However, discoloration was significantly more prevalent in the MTA group
(Abuelniel et al., 2021)/Egypt	RCT	60	Clinical carious exposure of the pulp and presence of bleeding upon exposure	Full pulpotomy	Biodentine™ and MTA	12	6	A high success was observed in both groups for all outcome measures for clinical success, with no significant difference between them. The mean survival time for the Biodentine™ and MTA groups was (17.8 and 18 months) with 95% confidence interval (17.4–18.2) and (18 .0–18.0) months respectively. Similarly, there were no significant differences between the Biodentine™ and MTA groups for radiographic success (P<0.001) with an increase in root length and increasing apical closure observed in both groups.
(Asgary et al., 2018)/ Iran	RCT	218	Vital mature permanent molar characterized by deep caries near the dental pulp.	Direct pulp caping, Full pulpotomy and Partial pulpotomy.	CEM	12	84	In deep caries management of mature permanent molars, the 4 VPTs were associated with favorable/comparable clinical and radiographic outcomes.
(Awawdeh et al., 2018)/Jordan	RCT	68	Reversible pulpitis based on the cold test, complaints of tooth pain, and radiographic finding	Full pulpotomy and Partial pulpotomy	Biodentine™ and MTA	12	15	Biodentine™ and MTA have favourable and comparable success rates when used as direct pulp capping or pulpotomy material in permanent mature teeth with carious exposure.

Study (Year)/ Location	Study Design	Number of teeth	Diagnosis	Intervention	Capping material	Follow-up (months)	Drop outs (lost patients)	Outcomes
(Bjorndal et al., 2010)/Denmark	RCT	58	Pulp was exposed as a result of the excavation of caries	Direct pulp caping and Partial pulpotomy	MTA	12	7	No significant difference in pulp vitality without apical radiolucency between the two capping procedures after more than 1 yr [31.8% and 34.5%; difference: 2.7%, 95% CI ()22.7; 26.6)]
(Brizuela et al., 2017)/Chile	RCT	169	Carious permanent tooth with pulpal exposure.	Direct pulp caping	Biodentine™ and MTA	12	100	There were no statistically significant differences among the experimental group.
(Hilton et al., 2013)/USA	RCT	401	Pulp exposure and pulp vitality.	Full pulpotomy	CH and MTA	12	43	This large randomized clinical trial provided confirmatory evidence for a superior performance with MTA as a direct pulp-capping agent as compared with CH when evaluated in a practice-based research network for up to 2 years
(Jang et al., 2015)/South Korea	RCT	46	Permanent teeth diagnosed with reversible pulpitis	Direct pulp capping	CEM and MTA	12	5	Both ProRoot MTA and Endocem exhibited similar cumulative successes as direct pulp capping materials up to 1 year.
(FA et al., 2017)/India	RCT	58	Bilateral asymptomatic first permanent molars with carious involvement	Direct pulp caping	Biodentine™ and MTA	12	16	This study reported 100% success rate with both MTA and Biodentine™ when used as direct pulp-capping agent in first permanent molars in 7- to 9-year-old children.
(Kundzina et al., 2017)/Norway	RCT	70	No history of pain or the presence of pain indicating, at most, reversible pulpitis	Direct pulp caping	CH and MTA	12	0	Mineral trioxide aggregate performed more effectively than a conventional CH liner as a direct pulp capping material in molars with carious pulpal exposure in adult patients.
(Nosrat et al., 2013)Iran	RCT	51	Immature molars with clinical carious exposure with	Full pulpotomy	CEM and MTA	12	2	Calcium-enriched mixture cement and MTA showed similar performance in pulpotomy of immature caries-exposed permanent molars

Study (Year)/ Location	Study Design	Number of teeth	Diagnosis	Intervention	Capping material	Follow-up (months)	Drop outs (lost patients)	Outcomes
(Özgür et al., 2017)/Turkey	RCT	80	Permanent first and second molar teeth with incomplete root formation and deep occlusal carious lesions	Partial pulpotomy	CH and MTA	12	4	Partial pulpotomy, performed with MTA or CH used as the pulp-capping material following hemostasis, provided comparable and favorable outcomes in carious pulp exposures of immature permanent teeth.
(Parinyaprom et al., 2018)Thailand	RCT	59	The tooth responded positively to cold test and no associated swelling, pus exudate, fistula, or abnormal mobility	Direct pulp caping	Biodentine™ and MTA	12	4	At mean follow-up of 18.9 12.9 months, the success rate was 92.6% with ProRoot MTA and 96.4% with Biodentine™ (P > .05; difference, 4%; 95% confidence interval [CI], –8% to 16%)
(Peskersoy et al., 2021)/Turkey	RCT	234	The tooth responded positively to cold test, with had deep Class II carious lesions.	Direct pulp caping	Biodentine™, CEM, CH and MTA	12	225	After 36-month follow-up, both MTA and Biodentine™ were found to be the appropriate material for direct pulp capping in permanent teeth.
(Suhag et al., 2019)/India	RCT	64	Teeth with carious pulp exposures and reversible pulpitis.	Direct pulp caping	CH and MTA	12	8	The success rate was 69% for CH and 93% for ProRoot MTA (p= .05). No significant difference in pain incidence was found between the 2 groups, although a significant pain reduction was found 6 hours after the procedure in both the groups. Significantly lower pain scores were reported in the MTA group (6.3 ± 9.5) compared with the CH group (18.5 ± 20.8) after 18 hours.
(Yang et al., 2020)/China	RCT	110	Immature permanent teeth with complicated crown fracture or complicated crown-root fracture.	Partial pulpotomy	CH and MTA	12	11	There were no intergroup differences in the survival rate, survival time, root length and dentin wall thickness. The calcific bridge was significantly thinner in the iRoot BP Plus group than in the calcium hydroxide group (0.97 ± 0.13 mm vs 1.36 ± 0.12 mm; F = 5.128, P = .029)

CEM: material based on calcium silicate; CH: calcium hydroxide; CI: confidence interval; MTA: mineral trioxide aggregate; RCT: Randomized clinical trial.

Risk of Bias

The bias analysis was performed considering the overall risk of bias as described in table 2, using the ROB2 tool resulted in 14 (87.5%) however only 8 studies (50%) had low risk of bias in all evaluated criteria, studies with low risk bias, 1 study (6.25%) considered an uncertain risk of bias and 1 study (6.25%) with high risk of bias, in figures 2 and 3, bias analysis is represented.

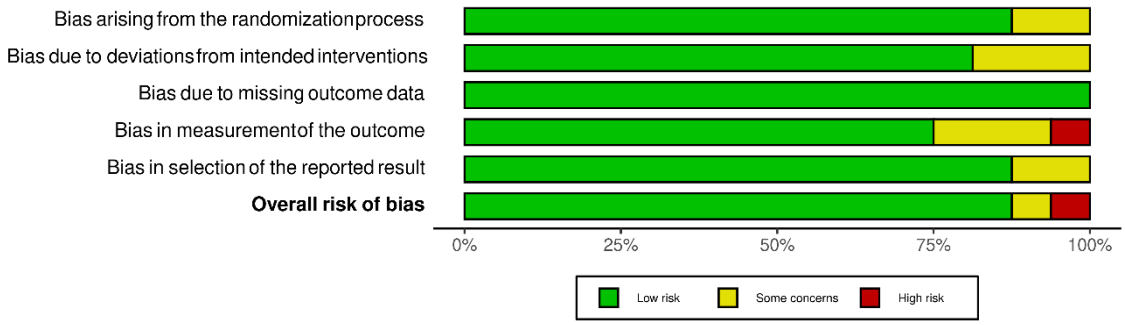

Figure 2: Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

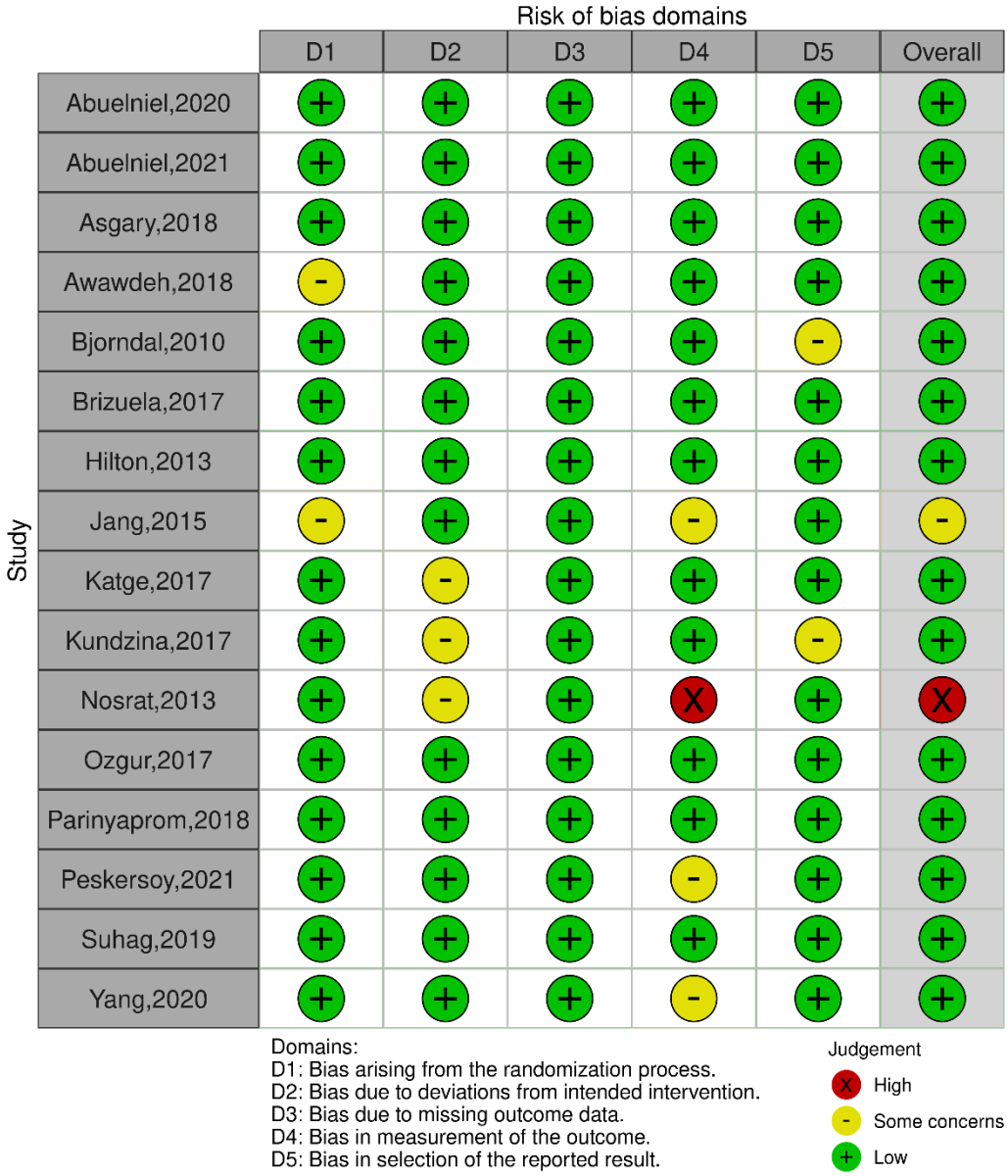

Figure 3: Risk of bias summary: review authors' judgements about each risk of bias item for each included study

Figure 4 shows the network plot of eligible comparisons where it is shown the result of the meta-analysis comparing DPC_Biodentine™ with DPC_MTA. The RCT data included in the network analysis are described in annex 1. The results of pairwise and network meta-analyses for all type of treatment are summarized in annex 1.

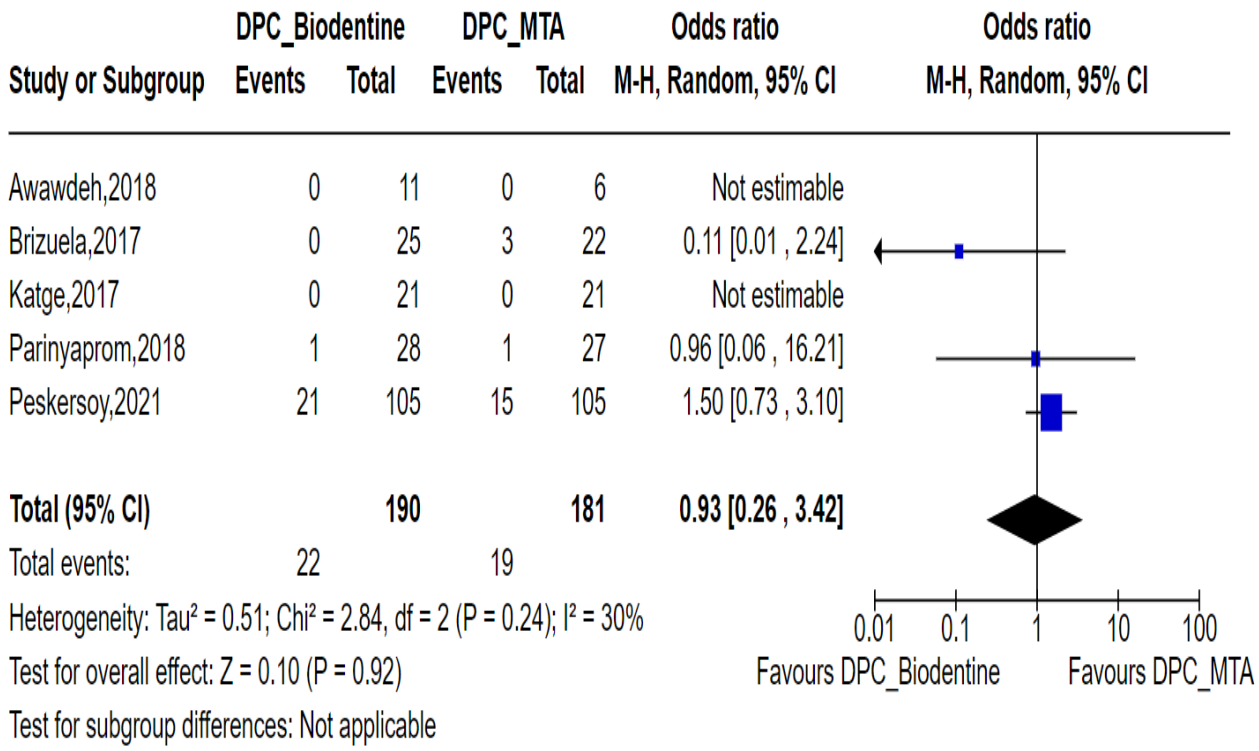

Figure 4: Meta-analysis comparing vital pulp treatment, direct pulp capping with Biodentine™ versus MTA, it is possible to observe that the difference between the materials is not significant and with moderate heterogeneity.

In figure 5 is represented the comparison between FP_Biodentine™ and FP_MTA where there is no statistically significant difference between the two materials (Biodentine™ and MTA) in the two treatment protocols (Capping direct pulp and total pulpotomy).

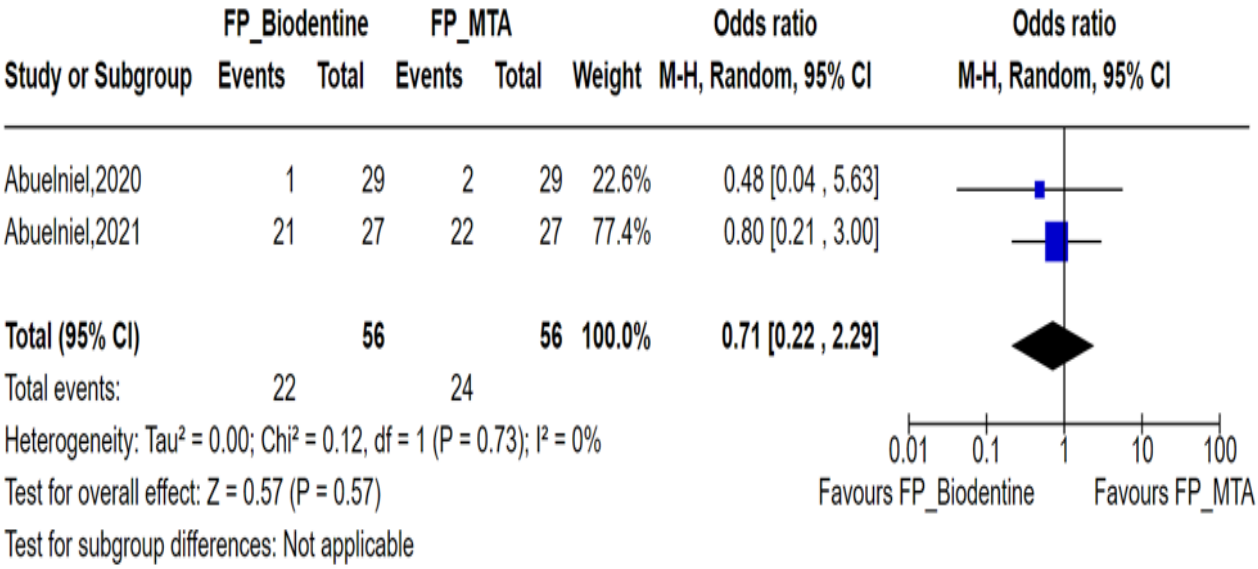

Figure 5: Meta-analysis comparing vital pulp treatment, full pulpotomy with Biodentine™ versus MTA, it is possible to observe that the difference between the materials is not significant and with a low heterogeneity

In the direct comparison between DPC_CH vs DPC_MTA, a significant difference between the materials used was obtained (figure 6), which is favourable for the use of MTA.

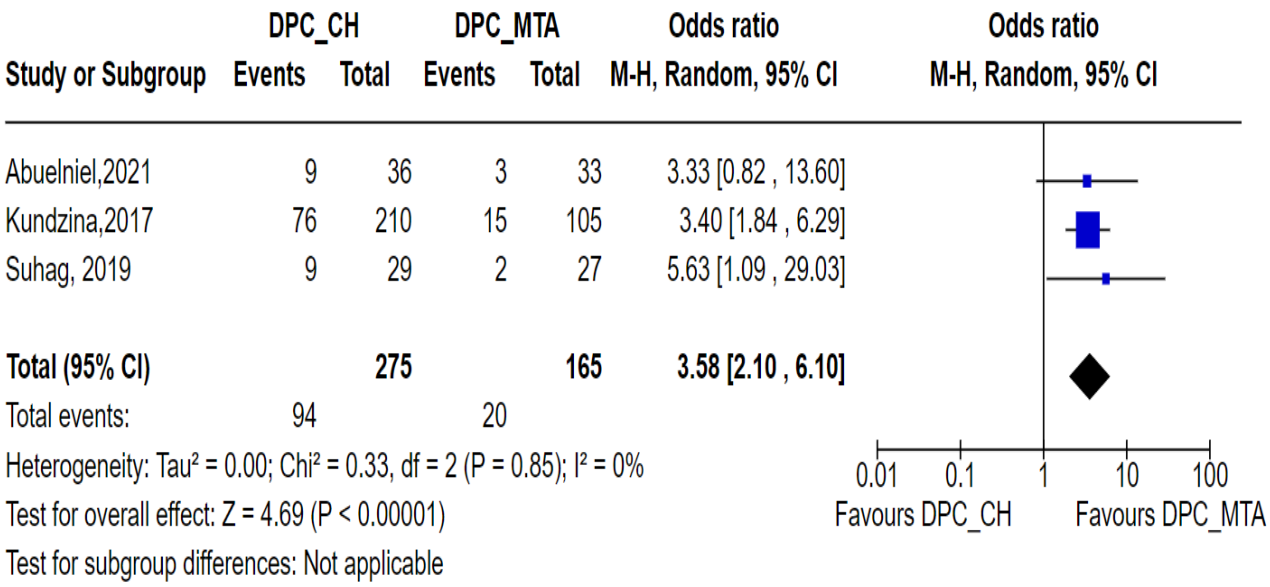

Figure 6: Meta-analysis comparing vital pulp treatment, direct pulp capping with CH versus MTA, it is possible to observe that the difference between the materials is significant for favours MTA and with a low heterogeneity.

On the other hand, the comparison between calcium hydroxide and MTA in partial pulpotomy did not result in a significant difference (figure 7). The comparison between DPC_Biodentine™ with DPC_MTA showed moderate heterogeneity (I^2 = 30%), while the comparisons between FP_Biodentine™ vs FP_MTA, DPC_CH vs DPC_MTA and PP_CH vs PP_MTA showed low heterogeneity (I^2 = 0% in both).

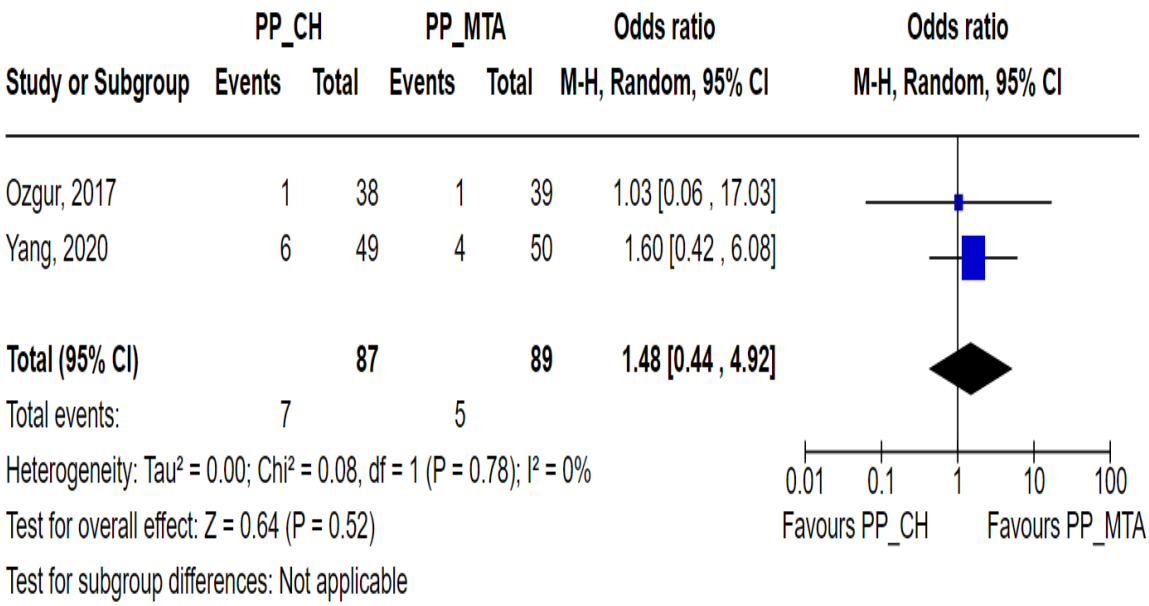

Figure 7: Meta-analysis comparing vital pulp treatment, partial pulpotomy with CH versus MTA, it is possible to observe that the difference between the materials is not significant with a low heterogeneity.

After loading the data into the Stata 17 database, using the odds ratio as a measure log. After setting up the data, the network interaction graph was generated to visualize the connection of the studies (figure 8), among the 12 interventions analysed or therapies that involve direct pulp capping were those that had the highest number of analysed teeth and the highest number of studies analysing the different treatment protocols, being the treatment with Direct pulp capping with MTA the most studied and compared with pulp capping with Biodentine™ and pulp capping with calcium hydroxide.

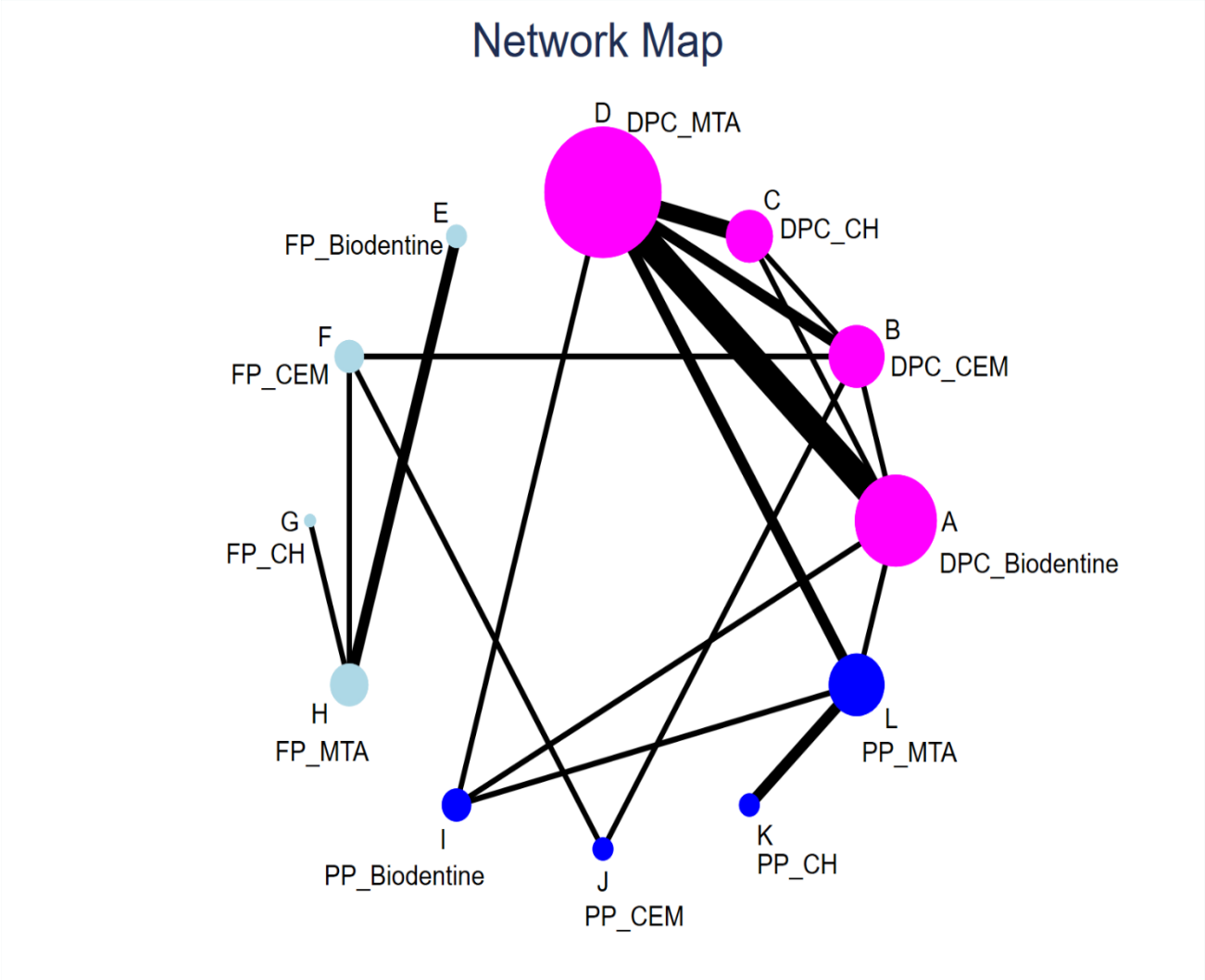

Figure 8: Network graph showing the direct relationship between the evaluated actions. The circle size is proportional to the number of patients randomized to each intervention and the line width is proportional to the number of studies that make each comparison. ***A: DPC_Biodentine™*** *(direct pulp capping using Biodentine™);* ***B: DPC_CEM*** *(direct pulp capping using material based on calcium silicate);* ***C: DPC_CH*** *(direct pulp capping using calcium hydroxide);* ***D: DPC_MTA*** *(direct pulp capping using mineral trioxide aggregate);* ***E: FP_Biodentine™*** *(full pulpotomy using Biodentine™);* ***F: FP_CEM*** *(full pulpotomy using material based on calcium silicate);* ***G: FP_CH*** *(full pulpotomy using calcium hydroxide);* ***H: FP_MTA*** *(direct full pulpotomy using mineral trioxide aggregate);* ***I: PP_Biodentine™*** *(partial pulpotomy using Biodentine™);* ***J: PP_CEM*** *(partial pulpotomy using material based on calcium silicate);* ***K: PP_CH*** *(partial pulpotomy using calcium hydroxide);* ***L: PP_MTA*** *(partial pulpotomy using mineral trioxide aggregate);* ***RCT*** *(root canal treatment).*

The results of the local inconsistency test and the results of the general inconsistency test (network meta inconsistency), listing the size of the differences for each treatment and the results of the statistical test, can be found in Appendix 2. In none of the treatments the inconsistency test showed statistical significance, with the global inconsistency presenting p = 0,79 and the local inconsistency test presenting p values between 0,166 and 0,992. As inconsistency was found absent in global and local tests, the consistency assumption was accepted, however in the analysis of local inconsistency it is possible to visualize a difference between data obtained from direct evidence and indirect evidence.

The probability of each treatment being considered the best option was estimated, using as parameters in the calculation of the probabilities assuming that the minimum was the best and with 10000 draws. The results suggest that full pulpotomy treatment with Biodentine™ has the higher odds of being the best treatment option in vital pulp therapy, followed by partial pulpotomy with MTA and direct pulp capping with MTA and full pulpotomy with MTA. When considering the probability of being the second best option, full pulpotomy with Biodentine™ has the higher odds, followed by full pulpotomy with MTA, partial pulpotomy with MTA and direct pulp capping with MTA, as shown in Figure 9.

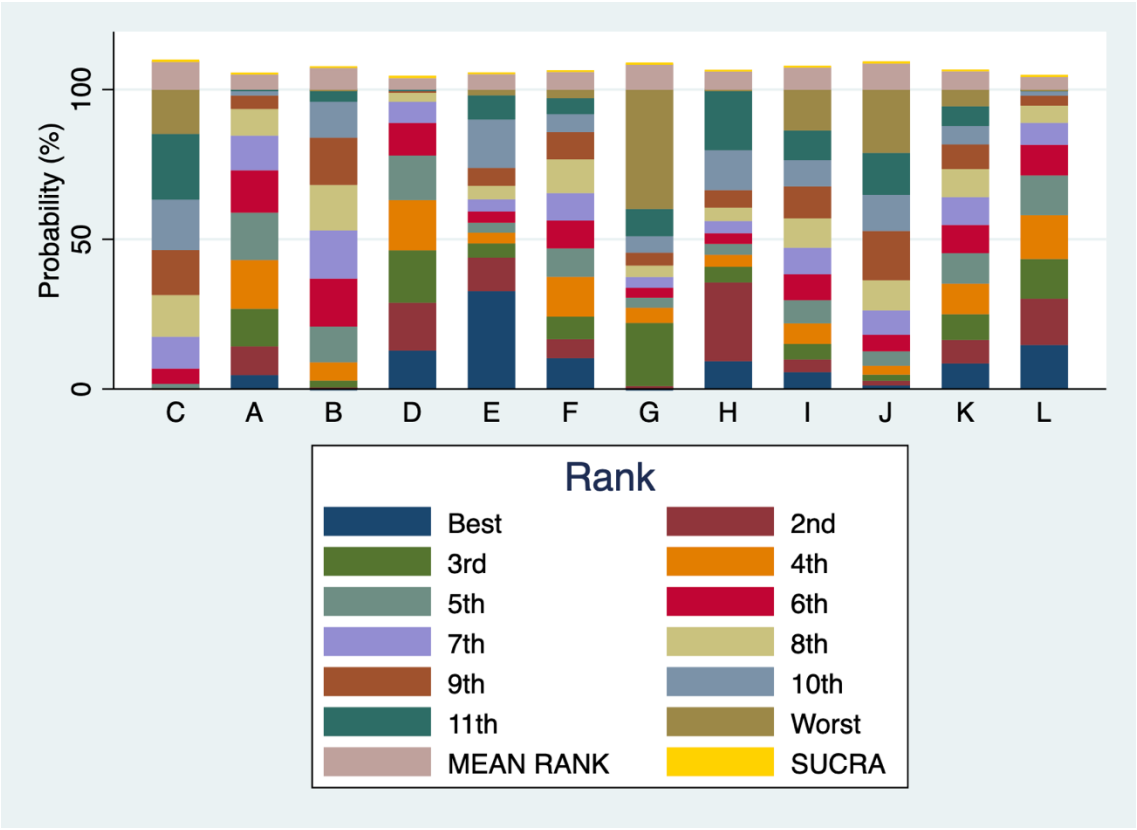

Figure 9: Chart of the probabilities of each treatment being the best option in relation to the other treatments is possible observe that the treatment with E is more likely to be the best option among the vital pulp therapy treatments. ***A: DPC_Biodentine™*** *(direct pulp capping using Biodentine™);* ***B: DPC_CEM*** *(direct pulp capping using material based on calcium silicate);* ***C: DPC_CH*** *(direct pulp capping using calcium hydroxide);* ***D: DPC_MTA*** *(direct pulp capping using mineral trioxide aggregate);* ***E: FP_Biodentine™*** *(full pulpotomy using Biodentine™);* ***F: FP_CEM*** *(full pulpotomy using material based on calcium silicate);* ***G: FP_CH*** *(full pulpotomy using calcium hydroxide);* ***H: FP_MTA*** *(direct full pulpotomy using mineral trioxide aggregate);* ***I: PP_Biodentine™*** *(partial pulpotomy using Biodentine™);* ***J: PP_CEM*** *(partial pulpotomy using material based on calcium silicate);* ***K: PP_CH*** *(partial pulpotomy using calcium hydroxide);* ***L: PP_MTA*** *(partial pulpotomy using calcium hydroxide).*

When comparing the treatments directly with the pulp capping with calcium hydroxide, a treatment in use for a long time and enshrined in the literature, it is possible to note that the treatment with pulp capping with MTA presents a significant result in relation to the treatment with calcium hydroxide, while the other treatments have non-significant effects when compared to direct pulp capping with calcium hydroxide (figure 10).

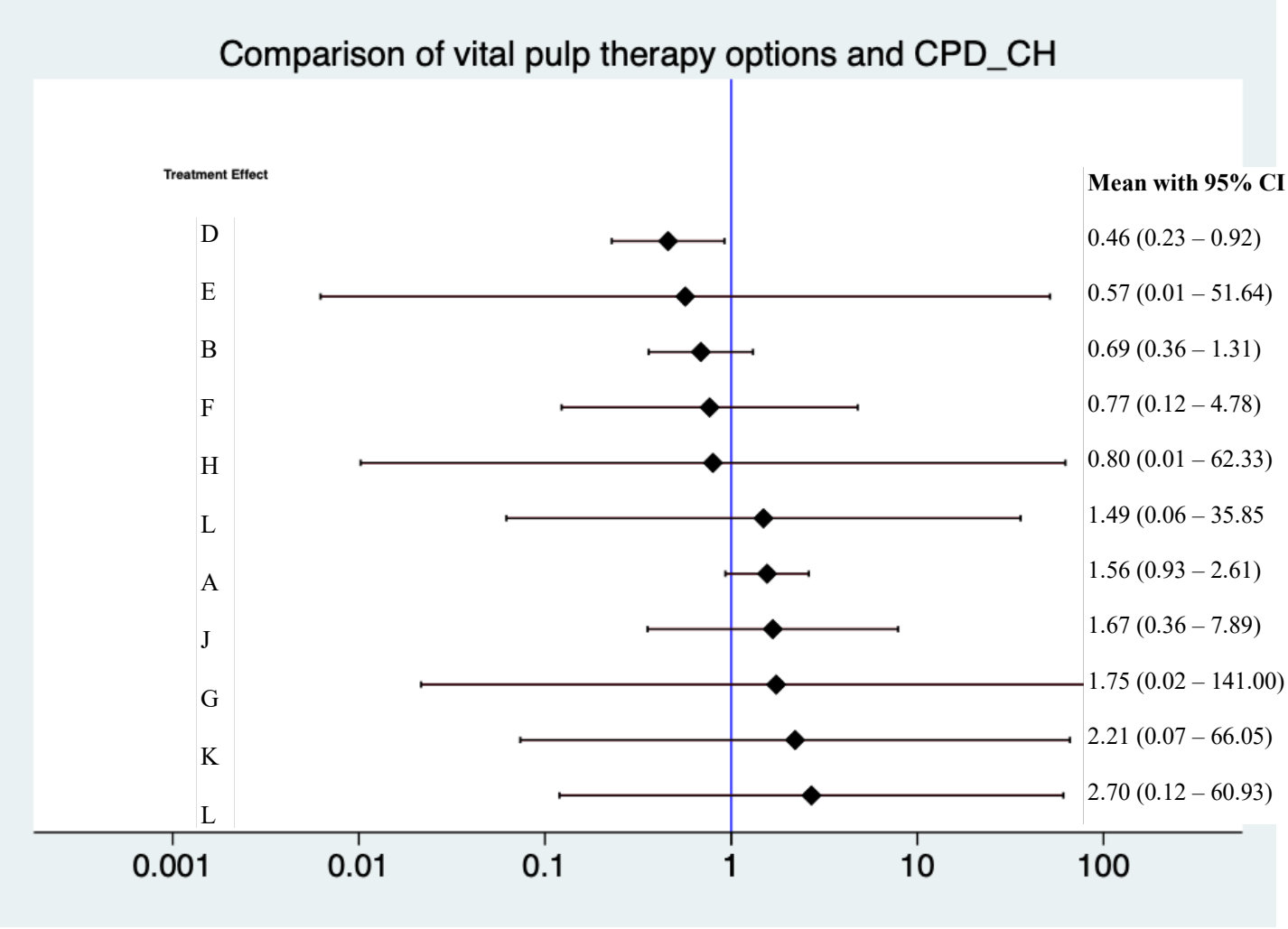

Figure 10: The treatment with pulp capping with MTA presented the best result when compared to all treatments with direct pulp capping with calcium hydroxide. ***A: DPC_Biodentine™*** *(direct pulp capping using Biodentine™);* ***B: DPC_CEM*** *(direct pulp capping using material based on calcium silicate);* ***C: DPC_CH*** *(direct pulp capping using calcium hydroxide);* ***D: DPC_MTA*** *(direct pulp capping using mineral trioxide aggregate);* ***E: FP_Biodentine™*** *(full pulpotomy using Biodentine™);* ***F: FP_CEM*** *(full pulpotomy using material based on calcium silicate);* ***G: FP_CH*** *(full pulpotomy using calcium hydroxide);* ***H: FP_MTA*** *(direct full pulpotomy using mineral trioxide aggregate);* ***I: PP_Biodentine™*** *(partial pulpotomy using Biodentine™);* ***J: PP_CEM*** *(partial pulpotomy using material based on calcium silicate);* ***K: PP_CH*** *(partial pulpotomy using calcium hydroxide);* ***L: PP_MTA*** *(partial pulpotomy using mineral trioxide aggregate)..*

IV. DISCUSSION

There is no consensus on the approach for treating teeth with pulp exposure (ESS 2019) and selective removal of carious tissue in deep carious lesions in order to avoid pulp exposure as a recommended approach (Schwendicke et al. 2016), however when pulpar exposition occurs, a conservative approach is indicated, with direct pulp capping being the most conservative and simplest approach available to maintain the pulp vital in cases of pulp exposure, as this approach does not result in the removal of pulp tissue as it occurs in partial and total pulpotomy.

This systematic review aimed to provide impartial and high-quality evidence on the results of direct pulp capping, partial pulpotomy and total pulpotomy, using calcium hydroxide and bioceramic cements MTA, Biodentine™ and CEM.

For the risk of bias analysis, the Cochane RoB2 tool was used and the results of the analysis of the studies demonstrate that, in general, the studies presented a low risk of bias, however, many studies have low methodological quality, which should be considered in the interpretation of the strength of the review results, especially with regard to the lack of a control group (a factor that makes it difficult to directly compare the techniques and materials available for vital pulp therapy).

Moreover, the data presented in the studies were obtained from clinical trials carried out mainly in a teaching environment in university clinics, with a very limited number of data obtained from trials carried out in General Practice settings. Future studies should adopt designs that take these issues into account and address other issues, including the adoption of specific inclusion criteria, adequate sample size (based on previous literature) and study design based on practicality and adequate follow-up time, since that in the long term the differences between treatments may become more evident, as evidenced in other studies that demonstrate bioceramics as a more interesting treatment option than calcium hydroxide.

Most studies compare Biodentine™, CEM, CH and MTA materials in direct pulp capping treatment, as can be seen in figure 8, where the line thickness shows the number

of studies and the circle size the number of patients allocated to each one of the treatments. In the comparison between the different treatments of vital pulp, the hydroxide capping represents the best treatment option, however the direct evidence of the comparison between the calcium hydroxide capping and the MTA capping revealed an advantage for the MTA as a better treatment option (figure 6). In the comparison between calcium hydroxide and MTA in partial pulpotomy, no significant difference was observed between the materials (figure 7). However, due to the small number of studies and the small size of the analyzed sample, these results must be viewed with caution and more studies must be conducted to verify the best therapeutic option. Based on our results, it is suggested that future studies use calcium hydroxide as a control group for the evaluation of other therapeutic options, as it is already known that calcium hydroxide is a biocompatible material and that it presents good results in these situations.

Treatments using calcium hydroxide (full pulpotomy and direct pulp capping, treament g and c respectively) as well as partial pulpotomy with CEM and Biodentine™, had the highest percentages of chance of being the best treatment option for vital pulp therapy (39.4%, 15.2%, 20.9% and 13.9% respectively).

In the analysis of direct evidence, the purchase between MTA and Calcium Hydroxide when used for direct pulp capping demonstrates an advantage for MTA (figure 6) while the comparison between MTA and Biodentine™ showed no significant difference between materials in direct pulp capping (figure 4).

This demonstrates that even with the emergence of new biomaterials for the treatment of teeth with vital pulp, calcium hydroxide remains a good option when analyzed over a period of one year, an option that has the advantage of having a reduced cost and has already been tested in several situations, always with good results.

Potential biases and limitations of the review

The network meta-analysis provides estimates directly and indirectly comparing evidence obtained from several different treatments, however these data are always statistical estimates, especially when no direct evidence to evaluate all analyzed treatments is available. Considering the full pulpotomy with calcium hydroxide, for

example, there is only direct evidence to compare it with full pulpotomy with MTA, so the results presented here mainly take into account evidence obtained indirectly, and should therefore be analyzed with caution.

This review was based on randomized clinical trials and sought to perform a meta-analysis of the data, even with an extensive literature search, relevant reports may not have been retrieved in the search. The goal of network analysis makes assumptions based on the direct relationships between the studies, however the small number of articles in various branches of the network can lead to inaccurate estimates of the results, taking into account that the methodology of the studies are not all the same and that pulp diagnoses are not clearly presented in all studies.

The limitations of the original studies evaluated will be reflected in the quality of this review, however, as the present results are based only on RCTs, it can be stated that the evidence presented here can be considered potentially high.

More studies with a rigorous design of pulp diagnosis and that seek to compare the different treatment modalities used in vital pulp therapy, as well as the different pulp protection materials and that preferentially use a control group that can serve as a common comparator between the different studies is desired to be able to really affirm the best therapeutic option for teeth with pulp vitality and that need conservative intervention. Studies with long-term follow-up are also valuable to verify the long-term response of these teeth, whether in the esthetic part with discoloration or even complications that may lead to the need for endodontic treatment.

V. CONCLUSION

Vital pulp treatments are an interesting treatment option that allows the maintenance of pulp vitality associated with good long-term results. The new biomaterials have been shown to be superior to the treatments already established, with MTA presenting good results both in direct pulp capping and in partial and total pulpotomy, with Biodentine™ presenting itself as the best result but only in total pulpotomy.

More studies are needed to be sure of the best therapeutic option for these cases, especially with evaluation of long-term results and with more comparisons between Biodentine™ and MTA in different treatments for vital pulp therapy.

New studies should take into account in the methodology the standardization of pulp diagnosis both pre-treatment and follow-up and an accurate description of the pulp diagnosis should be added to the reports, it is also important to compare different modality of vital pulp treatments (eg. direct pulp capping vs partial pulpotomy) with different materials and not just the same material.

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ANNEXES

Annex 1: *Excluded works and reasons for exclusion*

Author (YEAR)	Reason for exclusion
(Benoist et al., 2012)	I had no data according to the inclusion criteria
(Bjorndal et al., 2010)	I had no data according to the inclusion criteria
(Gurcan & Seymen, 2019)	Sample includes primary teeth
(Harms et al., 2019)	Non-randomized clinical trial
(Hegde et al., 2017)	Non-randomized clinical trial
(Lee et al., 2015)	The time of follow up is not adequate.
(Mahapatra et al., 2019)	Full text not recovered
(Noor et al., 2021)	Non-randomized clinical trial
(Nowicka et al., 2013)	The time of follow up is not adequate.
(Saeed Asgary, Eghbal, et al., 2017)	Full text not recovered
(Vu et al., 2020)	I had no data according to the inclusion criteria
(S Asgary et al., 2014)	I had no data according to the inclusion criteria
Song 2015	The time of follow up is not adequate.
Galani	I had no data according to the inclusion criteria
Asgary 2013	I had no data according to the inclusion criteria

Annex 2: Main data from the studies included in the review.

		1		2		3		4		5		6		7		8		9		10		11		12	
	Protocol	**A**		**B**		**C**		**D**		**E**		**F**		**G**		**H**		**I**		**J**		**K**		**L**	
		E	P	E	P	E	P	E	P	E	P	E	P	E	P	E	P	E	P	E	P	E	P	E	P
#	**Reference**																								
1	Abuelniel,2020									1	29					2	29								
2	Abuelniel,2021									21	27					22	27								
3	Asgary,2018			3	57							2	49							4	47				
4	Awawdeh,2018	0	11					0	6									3	23					2	28
5	Bjorndal,2010							15	22															19	29
6	Brizuela,2017	0	25					3	22																
7	Hilton,2013													45	175	25	183								
8	Jang,2015			3	18			3	23																
9	Katge,2017	0	21					0	21																
10	Kundzina,2017					9	36	3	33																
11	Nosrat,2013											0	25			0	24								
12	Ozgur,2017																					1	38	1	39
13	Parinyaprom,2018	1	28					1	27																
14	Peskersoy,2021	21	105	28	105	76	210	15	105																
15	Suhag,2019					9	29	2	27																
16	Yang,2020																					6	49	4	50

E: Eventes; **P**: Patients Protocol A: **DPC_Biodentine** (direct pulp capping using Biodentine); Protocol B: **DPC_CEM** (direct pulp capping using material based on calcium silicate); Protocol C: **DPC_CH** (direct pulp capping using calcium hydroxide); Protocol D: **DPC_MTA** (direct pulp capping using mineral trioxide aggregate); Protocol E: **FP_Biodentine** (full pulpotomy using Biodentine); Protocol F: **FP_CEM** (full pulpotomy using material based on calcium silicate); Protocol G: **FP_CH** (full pulpotomy using calcium hydroxide);Protocol H: **FP_MTA** (direct full pulpotomy using mineral trioxide aggregate); Protocol I: **PP_Biodentine** (partial pulpotomy using Biodentine); Protocol J: **PP_CEM** (partial pulpotomy using material based on calcium silicate); Protocol K: **PP_CH** (partial pulpotomy using calcium hydroxide); Protocol L: **PP_MTA** (partial pulpotomy using mineral trioxide aggregate).

Annex 3: *Results of network setup order. Protocol A:* ***DPC_Biodentine™*** *(direct pulp capping using Biodentine™); Protocol B:* ***DPC_CEM*** *(direct pulp capping using material based on calcium silicate); Protocol C:* ***DPC_CH*** *(direct pulp capping using calcium hydroxide); Protocol D:* ***DPC_MTA*** *(direct pulp capping using mineral trioxide aggregate); Protocol E:* ***FP_Biodentine™*** *(full pulpotomy using Biodentine™); Protocol F:* ***FP_CEM*** *(full pulpotomy using material based on calcium silicate); Protocol G:* ***FP_CH*** *(full pulpotomy using calcium hydroxide);Protocol H:* ***FP_MTA*** *(direct full pulpotomy using mineral trioxide aggregate); Protocol I:* ***PP_Biodentine™*** *(partial pulpotomy using Biodentine™); Protocol J:* ***PP_CEM*** *(partial pulpotomy using material based on calcium silicate); Protocol K:* ***PP_CH*** *(partial pulpotomy using calcium hydroxide); Protocol L:* ***PP_MTA*** *(partial pulpotomy using mineral trioxide aggregate).*

```
. network setup d n, studyvar(study)
Treatments used
   A (reference):                    a
   B:                                b
   C:                                c
   D:                                d
   E:                                e
   F:                                f
   G:                                g
   H:                                h
   I:                                i
   J:                                j
   K:                                k
   L:                                l

Measure                              Log odds ratio

Studies
   ID variable:                      study
   Number used:                      16
   IDs with zero cells:              4 6 9 11
   - count added to all their cells: .5
   IDs with augmented reference arm: 1 2 3 5 7 8 10 11 12 15 16
   - observations added:             0.001
   - mean in augmented observations: study-specific mean

Network information
   Components:                       1 (connected)
   D.f. for inconsistency:           5
   D.f. for heterogeneity:           5

Current data
   Data format:                      augmented
   Design variable:                  _design
   Estimate variables:               _y*
   Variance variables:               _S*
   Command to list the data:         list study _y* _S*, noo sepby(_design)

.
```

Annex 3: *Inconsistency test between direct and indirect treatment comparisons in mixed treatment comparison*

Protocol A: **DPC_Biodentine™** (direct pulp capping using Biodentine™); Protocol B: **DPC_CEM** (direct pulp capping using material based on calcium silicate); Protocol C: **DPC_CH** (direct pulp capping using calcium hydroxide); Protocol D: **DPC_MTA** (direct pulp capping using mineral trioxide aggregate); Protocol E: **FP_Biodentine™** (full pulpotomy using Biodentine™); Protocol F: **FP_CEM** (full pulpotomy using material based on calcium silicate); Protocol G: **FP_CH** (full pulpotomy using calcium hydroxide);Protocol H: **FP_MTA** (direct full pulpotomy using mineral trioxide aggregate); Protocol I: **PP_Biodentine™** (partial pulpotomy using Biodentine™); Protocol J: **PP_CEM** (partial pulpotomy using material based on calcium silicate); Protocol K: **PP_CH** (partial pulpotomy using calcium hydroxide); Protocol L: **PP_MTA** (partial pulpotomy using mineral trioxide aggregate).

```
. network sidesplit all

Side    Direct                Indirect              Difference
        Coef.      Std. Err.  Coef.      Std. Err.  Coef.      Std. Err.  P>|z|
C D *   -1.274635   .2718445   .5794581    1.27613  -1.854093   1.337214  0.166
A C      .8470331   .2810634   1.990028   .9248761  -1.142995   .9555729  0.232
A B      .3855224   .3288768   1.236919   1.196453  -.8513961    1.24144  0.493
A D *   -.2182898    .339664  -.2403747   .9616661    .022085   1.033196  0.983
A I *    1.367832   1.556101  -.7677898   2.273528   2.135622   3.330962  0.521
A L *    .7026112   1.513374  -.3923304   .6782411   1.094942   1.680413  0.515
B C      .4454971   .2622412   1.119532   .9561273  -.6740346   .9817591  0.492
B D *   -.7116856   .3299941  -.3201473   1.002695  -.3915383    1.07905  0.717
B F *   -.2666289   .9344132   .3740442   49.94023  -.6406731   49.94885  0.990
B J *     .515466   .7906375   1.722758   95.08226  -1.207292   95.08637  0.990
D I *    .7972874   1.577448   .7670391   2.198165   .0302483   3.310434  0.993
D L *   -.0804901    .563689   2.054286    3.21519  -2.134776   3.327962  0.521
E H *    .3420915   .5964469  -1.439661   137.6867   1.781752    137.688  0.990
F H *    .0400053   2.019909   .6828382   51.76586  -.6428329   51.80525  0.990
F J *    .7820947   .8913655  -.4920345   101.6648   1.274129   101.6712  0.990
G H *   -.7828473   .2761225  -1.347444    159.545   .5645967   159.5453  0.997
I L *   -.5931921   .8787665  -2.066199   2.562124   1.473006   2.746487  0.592
K L *   -.3909937   .6139362  -2.244982    185.737   1.853988   185.7383  0.992

* Warning: all the evidence about these contrasts comes from the trials which directly
> compare them.
```

```
. network meta consistency
Command is: mvmeta _y _S  , bscovariance(exch 0.5) longparm suppress(uv mm)  vars(_y_A
> _y_B _y_D _y_E _y_F _y_G _y_H _y_I _y_J _y_K _y_L)
Note: using method reml
Note: using variables _y_A _y_B _y_D _y_E _y_F _y_G _y_H _y_I _y_J _y_K _y_L
Note: 16 observations on 11 variables
Note: variance-covariance matrix is proportional to .5*I(11)+.5*J(11,11,1)

initial:       log likelihood =  -91.39637
rescale:       log likelihood = -91.103159
rescale eq:    log likelihood =  -89.90283
Iteration 0:   log likelihood =  -89.90283  (not concave)
Iteration 1:   log likelihood = -88.886859
Iteration 2:   log likelihood = -88.791344
Iteration 3:   log likelihood =  -88.79134

Multivariate meta-analysis
Variance-covariance matrix = proportional .5*I(11)+.5*J(11,11,1)
Method = reml                                   Number of dimensions    =    11
Restricted log likelihood = -88.79134           Number of observations  =    16
```

		Coefficient	Std. err.	z	P>|z|	[95% conf.	interval]
_y_A	_cons	-.9326017	.2718067	-3.43	0.001	-1.465333	-.3998703
_y_B	_cons	-.4869105	.2552093	-1.91	0.056	-.9871116	.0132906
_y_D	_cons	-1.153562	.2574384	-4.48	0.000	-1.658132	-.6489921
_y_E	_cons	-1.054393	2.31608	-0.46	0.649	-5.593826	3.48504
_y_F	_cons	-.7533167	.9684584	-0.78	0.437	-2.65146	1.144827
_y_G	_cons	.0705151	2.254999	0.03	0.975	-4.349202	4.490232
_y_H	_cons	-.7123342	2.238046	-0.32	0.750	-5.098824	3.674156
_y_I	_cons	-.3681645	.9171846	-0.40	0.688	-2.165813	1.429484
_y_J	_cons	.0286494	.8307613	0.03	0.972	-1.599613	1.656912
_y_K	_cons	-.7412987	.8524283	-0.87	0.385	-2.412028	.9294301
_y_L	_cons	-1.132316	.5913875	-1.91	0.056	-2.291414	.0267827

Estimated between-studies SDs and correlation matrix:

	SD	_y_A	_y_B	_y_D	_y_E	_y_F	_y_G
_y_A	1.597e-07	1	.	.	.	.	.
_y_B	1.597e-07	.5	1	.	.	.	.
_y_D	1.597e-07	.5	.5	1	.	.	.
_y_E	1.597e-07	.5	.5	.5	1	.	.
_y_F	1.597e-07	.5	.5	.5	.5	1	.
_y_G	1.597e-07	.5	.5	.5	.5	.5	1
_y_H	1.597e-07	.5	.5	.5	.5	.5	.5
_y_I	1.597e-07	.5	.5	.5	.5	.5	.5
_y_J	1.597e-07	.5	.5	.5	.5	.5	.5
_y_K	1.597e-07	.5	.5	.5	.5	.5	.5
_y_L	1.597e-07	.5	.5	.5	.5	.5	.5

	_y_H	_y_I	_y_J	_y_K	_y_L
_y_A	.	.	.	.	.
_y_B	.	.	.	.	.
_y_D	.	.	.	.	.
_y_E	.	.	.	.	.
_y_F	.	.	.	.	.
_y_G	.	.	.	.	.
_y_H	1	.	.	.	.
_y_I	.5	1	.	.	.
_y_J	.5	.5	1	.	.
_y_K	.5	.5	.5	1	.
_y_L	.5	.5	.5	.5	1

```
. network meta inconsistency
Command is: mvmeta _y _S  , bscovariance(exch 0.5) longparm suppress(uv mm) eq(_y_D: des_AD des_ADIL des_BD des_CD, _y_L: des_DL) vars(_y_A _y_B _y_D _y_E _y_F
> _y_G _y_H _y_I _y_J _y_K _y_L)
Note: using method reml
Note: regressing _y_A on (nothing)
Note: regressing _y_B on (nothing)
Note: regressing _y_D on des_AD des_ADIL des_BD des_CD
Note: regressing _y_E on (nothing)
Note: regressing _y_F on (nothing)
Note: regressing _y_G on (nothing)
Note: regressing _y_H on (nothing)
Note: regressing _y_I on (nothing)
Note: regressing _y_J on (nothing)
Note: regressing _y_K on (nothing)
Note: regressing _y_L on des_DL
Note: 16 observations on 11 variables
Note: variance-covariance matrix is proportional to .5*I(11)+.5*J(11,11,1)

initial:       log likelihood = -83.597513
rescale:       log likelihood = -83.597513
rescale eq:    log likelihood = -82.478299
Iteration 0:   log likelihood = -82.478299  (not concave)
Iteration 1:   log likelihood = -82.465829
Iteration 2:   log likelihood = -82.465499
Iteration 3:   log likelihood = -82.465499

Multivariate meta-analysis
Variance-covariance matrix = proportional .5*I(11)+.5*J(11,11,1)
Method = reml                               Number of dimensions    =    11
Restricted log likelihood = -82.465499      Number of observations  =    16
```

```
Multivariate meta-analysis
Variance-covariance matrix = proportional .5*I(11)+.5*J(11,11,1)
Method = reml                                 Number of dimensions    =    11
Restricted log likelihood = -82.465499        Number of observations  =    16
```

	Coefficient	Std. err.	z	P>|z|	[95% conf.	interval]
_y_A						
_cons	-.8191726	.2830934	-2.89	0.004	-1.374026	-.2643196
_y_B						
_cons	-.4444654	.2632849	-1.69	0.091	-.9604943	.0715634
_y_D						
des_AD	1.233747	1.00454	1.23	0.219	-.7351155	3.202609
des_ADIL	.9759346	2.092167	0.47	0.641	-3.124638	5.076507
des_BD	.4924998	.9538264	0.52	0.606	-1.376966	2.361965
des_CD	-.2008952	.6286824	-0.32	0.749	-1.43309	1.0313
_cons	-1.224617	.3136811	-3.90	0.000	-1.839421	-.6098137
_y_E						
_cons	-1.01203	2.316978	-0.44	0.662	-5.553224	3.529164
_y_F						
_cons	-.7108867	.9706162	-0.73	0.464	-2.613259	1.191486
_y_G						
_cons	.1128797	2.255922	0.05	0.960	-4.308646	4.534406
_y_H						
_cons	-.6699693	2.238976	-0.30	0.765	-5.058282	3.718343
_y_I						
_cons	.5486047	1.58134	0.35	0.729	-2.550765	3.647975
_y_J						
_cons	.0710879	.8332768	0.09	0.932	-1.562105	1.70428
_y_K						
_cons	.346394	1.726389	0.20	0.841	-3.037266	3.730054
_y_L						
des_DL	-1.300248	1.738664	-0.75	0.455	-4.707966	2.10747
_cons	-.0445956	1.613579	-0.03	0.978	-3.207151	3.11796

```
Estimated between-studies SDs and correlation matrix:
```

	SD	_y_A	_y_B	_y_D	_y_E	_y_F	_y_G	_y_H	_y_I	_y_J	_y_K	_y_L
_y_A	1.713e-09	1	.	.	.	.	.	.	.	.	.	.
_y_B	1.713e-09	.5	1	.	.	.	.	.	.	.	.	.
_y_D	1.713e-09	.5	.5	1	.	.	.	.	.	.	.	.
_y_E	1.713e-09	.5	.5	.5	1	.	.	.	.	.	.	.
_y_F	1.713e-09	.5	.5	.5	.5	1	.	.	.	.	.	.
_y_G	1.713e-09	.5	.5	.5	.5	.5	1	.	.	.	.	.
_y_H	1.713e-09	.5	.5	.5	.5	.5	.5	1	.	.	.	.
_y_I	1.713e-09	.5	.5	.5	.5	.5	.5	.5	1	.	.	.
_y_J	1.713e-09	.5	.5	.5	.5	.5	.5	.5	.5	1	.	.
_y_K	1.713e-09	.5	.5	.5	.5	.5	.5	.5	.5	.5	1	.
_y_L	1.713e-09	.5	.5	.5	.5	.5	.5	.5	.5	.5	.5	1

```
Testing for inconsistency:
 ( 1)  [_y_D]des_AD = 0
 ( 2)  [_y_D]des_ADIL = 0
 ( 3)  [_y_D]des_BD = 0
 ( 4)  [_y_D]des_CD = 0
 ( 5)  [_y_L]des_DL = 0

         chi2(  5) =    2.41
       Prob > chi2 =    0.7900
mvmeta command stored as F9; test command stored as F8
```

Annex 4:: *Estimated probabilities (%) of each treatment being the best.*

Protocol A: **DPC_Biodentine™** (direct pulp capping using Biodentine™); Protocol B: **DPC_CEM** (direct pulp capping using material based on calcium silicate); Protocol C: **DPC_CH** (direct pulp capping using calcium hydroxide); Protocol D: **DPC_MTA** (direct pulp capping using mineral trioxide aggregate); Protocol E: **FP_Biodentine™** (full pulpotomy using Biodentine™); Protocol F: **FP_CEM** (full pulpotomy using material based on calcium silicate); Protocol G: **FP_CH** (full pulpotomy using calcium hydroxide);Protocol H: **FP_MTA** (direct full pulpotomy using mineral trioxide aggregate); Protocol I: **PP_Biodentine™** (partial pulpotomy using Biodentine™); Protocol J: **PP_CEM** (partial pulpotomy using material based on calcium silicate); Protocol K: **PP_CH** (partial pulpotomy using calcium hydroxide); Protocol L: **PP_MTA** (partial pulpotomy using mineral trioxide aggregate).

```
. network rank min, all line cumulative seed (10000) reps (10000) meanrank
Command is: mvmeta, noest pbest(min  in 1, zero id(study) all line cumulative seed(1000
> 0) reps(10000) meanrank stripprefix(_y_) zeroname(C) rename(A = A, B = B, C = C, D =
> D, E = E, F = F, G = G, H = H, I = I, J = J, K = K, L = L))

Estimated probabilities (%) of each treatment being the best (and other ranks)
- assuming the minimum parameter is the best
- using 10000 draws
- allowing for parameter uncertainty
```

study and Rank	Treatment											
	C	A	B	D	E	F	G	H	I	J	K	L
1												
Best	0.0	4.7	0.1	12.9	32.7	10.3	0.0	9.4	5.6	1.2	8.6	14.7
2nd	0.0	9.6	0.5	16.0	11.2	6.4	1.0	26.2	4.3	1.6	7.9	15.5
3rd	0.0	12.6	2.3	17.5	4.8	7.5	21.1	5.2	5.2	2.0	8.6	13.3
4th	0.2	16.2	6.1	16.8	3.6	13.3	5.1	4.0	6.9	3.0	10.2	14.6
5th	1.5	15.9	11.9	14.9	3.3	9.5	3.4	3.6	7.7	4.8	10.2	13.3
6th	5.2	14.1	16.1	10.9	3.8	9.3	3.2	3.6	8.7	5.5	9.4	10.2
7th	10.6	11.6	16.1	7.0	4.1	9.2	3.7	4.1	8.9	8.2	9.3	7.4
8th	13.9	8.9	15.2	3.0	4.5	11.2	3.8	4.5	9.8	10.1	9.3	5.7
9th	15.0	4.5	15.8	0.9	6.0	9.1	4.3	5.8	10.7	16.5	8.3	3.3
10th	16.9	1.6	12.0	0.2	16.2	6.0	5.5	13.3	8.8	12.0	6.2	1.5
11th	21.9	0.4	3.9	0.0	8.1	5.3	9.1	20.2	9.9	14.0	6.6	0.6
Worst	14.8	0.0	0.2	0.0	1.9	2.9	39.9	0.0	13.7	21.1	5.6	0.0
MEAN RANK	9.5	5.0	7.3	3.9	5.1	5.9	8.5	6.1	7.4	8.9	6.1	4.2
SUCRA	0.2	0.6	0.4	0.7	0.6	0.6	0.3	0.5	0.4	0.3	0.5	0.7