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REVIEW ARTICLE

Effectiveness of revitalization in treating apical periodontitis: A systematic review and meta-analysis

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Abstract

Background: Revitalization procedures primarily aim to eliminate clinical symptoms and heal periapical lesions.

Objectives: The objective of the study was to elucidate the effectiveness of revitalization in treating apical periodontitis in necrotic mature and immature permanent teeth based on the following PICO question: In patients with permanent immature or mature teeth and pulp necrosis with or without signs of apical periodontitis (P) what is the effectiveness of revitalization (I) in comparison with calcium hydroxide apexification, apical plug and root canal treatment (C) in terms of tooth survival, pain, tenderness, swelling, need for medication (analgesics and antibiotics), radiographic evidence of reduction of apical lesion size, radiographic evidence of normal periodontal ligament space, radiographic evidence of increased root thickness and length (not for mature teeth), tooth function (fracture and restoration longevity), need for further intervention, adverse effects (including exacerbation, restoration integrity, allergy and discolouration), oral health-related quality of life (OHRQoL), presence of sinus tract and response to sensibility testing (O). (T) = Defined as a minimum of 1 year and maximum of as long as possible for all outcome measures, except 'pain, tenderness, swelling, need for medication (analgesics)', which is a minimum of 7 days and maximum of 3 months and OHRQoL which is minimum of 6 months and a maximum of as long as possible.

Methods: Three databases (PubMed, Embase and Cochrane Library) were searched for human, experimental and observational studies in English, complemented with hand search, until 31/10/2021. Studies recruiting teeth with pulp necrosis (with/without apical periodontitis), with minimum 10 teeth/arm at the end of the study and with a follow-up of at least 1 year, were included. Records without an abstract and a full text were excluded. The qualitative analysis of the included (non-) randomized controlled clinical trials was performed with the Revised Cochrane risk-of-bias tools (RoB 2 and ROBINS-I). Meta-analysis for survival and success (including a subgroup analysis for mature/immature permanent teeth) was performed using the Mantel–Haenszel method. The certainty of evidence was assessed using GRADE (Grades of Recommendation, Assessment, Development and Evaluation).

Results: From the 365 identified records, five met the inclusion criteria. The 12 months survival rate was 100% for all (im)mature permanent teeth in all groups

(3 studies). The success rate at 12 months was 100% for immature permanent teeth for I and C (1 study), however, reduced to 92% and 80% for mature teeth in I and C respectively (1 study, $p > .05$). The risk of bias for the most critical outcome (survival) was high for two studies and low for one. For the critical outcome success, all assessed studies were highly biased. Meta-analyses provided pooled relative risk with no statistically significant difference between I and C for both survival (RR = 1.00, 95%CI = 0.96–1.04, $p = 1.00$) and success (RR = 1.06; 95%CI = 0.83–1.35, $p = .66$). The evidence level for survival was kept 'low' and for success was downgraded to 'very low' due to inconsistency and imprecision.

Discussion: The survival and success rates were favourable in all included studies and for all groups; however, these outcomes are not reliable due to the low certainty level. Clinically, the most reported adverse event was tooth discolouration, hence the application of bismuth oxide containing calcium silicate cements should be avoided in revitalization. Radiographically, caution is needed when assessing periapical bone healing and further root development with periapical radiographs, due to multifactorial inaccuracies of this imaging technique. Methodological and assessment concerns need to be addressed in future clinical trials. Long-term results are necessary for studies reporting revitalization of mature permanent teeth, as they seem to be experimental so far.

Conclusions: No robust evidence was discovered to support that revitalization is effective to treat apical periodontitis in (im)mature permanent teeth. The success and survival rates of revitalized and fully pulpectomized (im)mature permanent teeth did not differ significantly.

Registration: Prospero: CRD42021262466.

KEYWORDS

dental pulp, nonvital teeth, permanent dentition, pulp necrosis, regenerative medicine, root canal therapy

INTRODUCTION

Dentine and pulp are histologically different structures that react to stimuli as one functional unit: the pulp–dentine complex. It regulates dentinogenesis and pulp vitality throughout life. Thus, it is important to understand the pathobiology of pulp and dentine (Pashley & Tay, 2012). However, when damaged, the regenerative and reparative capacity of pulp and dentine are limited (Pashley & Tay, 2012). Regenerated dentine has a greater ability to protect the pulp against bacterial and physicochemical insults than does any restorative or reparative material (Smith et al., 2000). Hence, regenerative medicine aims to boost regenerative wound healing, based on tissue engineering principles, from which the foundation was provided by Langer and Vacanti in 1993 (Langer & Vacanti, 1993; Murray et al., 2007). Increased knowledge in wound healing of dento-alveolar structures has led to biologically based therapies that favour tissue regeneration (Langer & Vacanti, 1993; Lin & Rosenberg, 2011; Murray et al., 2007). Consequently, since the last 15 years, a novel endodontic treatment modality named revitalization (also known as regenerative endodontic procedures or revascularization) attempts to cure inflamed or necrotic (im)mature permanent teeth by respecting the biology of the pulp–dentine complex (Diogenes et al., 2013; Galler et al., 2016; Wigler et al., 2013). The main idea behind revitalization is to firstly disinfect the root canal and subsequently attract (homing) or transplant mesenchymal stem cells from the (remaining) dental pulp and apical papilla (in case of immature teeth) into the root canal (Diogenes et al., 2013; Hilkens et al., 2015; Palma et al., 2019b). More specifically, this therapy is not based on mechanical and (aggressive) chemical debridement as in conventional root canal treatment but is supported by the pillars of tissue engineering: stem cells, growth factors and a scaffold (Galler et al., 2016; Hilkens et al., 2015).

Clinically, revitalization has been reported in trials mainly applying the cell homing concept (Lin et al., 2021; Torabinejad et al., 2017). Furthermore, this concept formed the basis for the clinical considerations and a position statement regarding revitalization procedures, described by the American Association of Endodontists (AAE)[1] and the European Society of Endodontology (ESE) respectively (Galler et al., 2016). Further root development in immature permanent teeth and regaining/maintaining pulp sensitivity are important objectives in revitalization. However, the primary goal is the elimination of symptoms and healing of the periapical lesion (if one is present) (Galler et al., 2016). In a previous systematic review, high pooled survival (97.8%; average follow-up: 16.7 months) and success (91.3%) rates for periapical bone healing were reported (Torabinejad et al., 2017). Nevertheless, reports since then were not consistent and in accordance with this outcome. A prospective clinical trial concerning the impact of apical periodontitis (AP) on revitalization of immature permanent teeth reported the negative impact of preoperative pulp necrosis and AP on further root development and complete periapical bone healing post revitalization (Shetty et al., 2020). In another study, the impact of the microbial load on the revitalization outcome was assessed (De-Jesus-Soares et al., 2020). In that study, the clinical symptoms and periapical lesions were successfully cured post-revitalization. Nevertheless, due to residual bacteria, the dentinal wall thickness was reduced. Furthermore, as there is a lack of mechanical debridement in revitalization, an *in vitro* study reported the detrimental role of a residual biofilm on the release of TGF-β1 after dentin conditioning (Cameron et al., 2019). Moreover, in revitalization cases with a persistent infection, longer periods of disinfection may lead to clinical success but histologically to rather repair than regeneration (Lui et al., 2020).

Unlike revitalization in immature teeth, where it is known that root development and the elimination of symptoms and signs of the periapical lesion are attainable, to our knowledge, no guidelines nor position statements recommend revitalization as a treatment option for mature permanent teeth with pulp necrosis. Nevertheless, a recent systematic review provided moderate-quality evidence regarding revitalization instead of conventional root canal treatment of mature permanent teeth with periapical lesions. Even if this approach seems experimental, the clinical outcomes seem promising (Glynis et al., 2021). Nevertheless, an independent analysis of survival and treatment success in immature and mature teeth should be carried out.

Clearly, infection control and morbidity caused by infection remain hurdles for this novel endodontic treatment modality. Hence, this systematic review primarily aims to elucidate the effectiveness of revitalization in treating AP in necrotic mature and immature permanent teeth.

METHODS

This review was conducted in accordance with the 'Preferred Reporting Items for Systematic reviews and Meta-Analyses' (PRISMA) and is registered on the PROSPERO database[2] with number CRD42021262466 (Moher et al., 2009).

Problem specification

The following review question was formulated: 'In patients with permanent immature or mature teeth and pulp necrosis with or without signs of AP, what is the effectiveness of revitalization in comparison with calcium hydroxide apexification, apical plug and root canal treatment in terms of tooth survival, pain, tenderness, swelling, need for medication, radiographic evidence of reduction of apical lesion size, radiographic evidence of normal periodontal ligament space, radiographic evidence of increased root thickness and length, tooth function, need for further intervention, adverse effects, oral health-related quality of life (OHRQoL), presence of sinus tract and response to sensibility testing'. In Table 1 the importance of the outcomes has been subdivided and expressed as a PICO question. Furthermore, in this context the term 'apical periodontitis (AP)' was defined prior to literature search: AP is a common global disease affecting the tissues surrounding the roots of teeth with infections within the root canal system. AP can be subdivided into[3]:

- asymptomatic AP—Inflammation and destruction of apical periodontium that is of pulpal origin, appears as an apical radiolucent area and does not produce clinical symptoms.
- symptomatic AP—Inflammation usually of the apical periodontium, producing clinical symptoms including a painful response to biting and/or percussion or palpation. It might or might not be associated with an apical radiolucent area.

Literature search plan

A comprehensive electronic literature search was performed in three databases (PubMed, Embase and Cochrane Library). The MeSH/Emtree terms and text words applied during the literature search and the search strategy are mentioned in Table 1. Additionally, a hand search was executed in the

TABLE 1 PICO question, search strategy and eligibility criteria

PICO question	P = patients with permanent immature or mature teeth and pulp necrosis with or without signs of AP I = individuals undergoing revitalization (regenerative endodontic procedures) in teeth with pulp necrosis with or without signs of AP C = individuals undergoing calcium hydroxide apexification, apical plug or root canal treatment in teeth with pulp necrosis with or without signs of AP O = *most critical*: tooth survival *critical*: pain, tenderness, swelling, need for medication (analgesics and antibiotics), radiographic evidence of reduction of apical lesion size, radiographic evidence of normal periodontal ligament space, radiographic evidence of increased root thickness and length (not for mature teeth) *additional*: tooth function (fracture and restoration longevity), need for further intervention, adverse effects (including exacerbation, restoration integrity, allergy and discolouration), OHRQoL, presence of sinus tract and response to sensibility testing
Databases	PubMed, Embase and Cochrane Library
Search strategy	
I	(1) MeSH/Emtree terms: 'dental pulp' OR 'medicine, regenerative' OR 'nerve regeneration' OR 'regenerative endodontics' OR 'regenerative medicine' OR 'regenerative medicines' OR 'revascularization' OR 'root canal therapy' OR Text words: 'dental pulp' OR 'dental pulp regeneration' OR 'medicine, regenerative' OR 'nerve regeneration' OR 'regenerative endodontics' OR 'regenerative endodontic procedure' OR 'regenerative medicine' OR 'regenerative medicines' OR 'revascularisation' OR 'revascularization' OR 'revitalisation' OR 'revitalization' OR 'root canal therapy' OR 'root canal therapies'
P	(2a) MeSH/Emtree terms: 'adult dentition' OR 'dentition, adult' OR 'permanent dentition' OR 'permanent tooth' OR 'secondary dentition' OR Text words: 'adult dentition' OR 'permanent tooth' OR immature' OR 'immature permanent tooth' OR 'immature permanent teeth' OR 'mature' OR 'mature permanent tooth' OR 'mature permanent teeth' OR 'permanent dentition' OR 'permanent teeth' (2b) MeSH/Emtree terms: 'dental' OR 'dental pulp necrosis' OR 'dental pulp necroses' OR 'necrosis' OR 'nonvital teeth' OR 'nonvital tooth' OR 'pulp necrosis' OR 'pulp necroses, dental' OR 'pulp necroses' OR 'teeth, nonvital' OR 'tooth, nonvital' OR Text words: 'nonvital' OR 'nonvital' OR 'nonvital' OR 'nonvital tooth' OR 'necrosis'OR 'necrotic' OR 'necrotic pulp' OR 'pulp necrosis'
Search combination	(1) **AND** (2a **AND** 2b)
Inclusion criteria	• Language: English • Study designs: human, experimental ((non-)randomized controlled clinical trials) and longitudinal observational studies (retrospective and prospective comparative cohort and case–control studies) • Teeth with pulp necrosis (with/without AP) are included • Number of teeth: at least 20 (10 in each arm) at the end of the study • Duration of follow-up: minimum of 1 year and maximum of as long as possible for all outcome measures, except 'pain, tenderness, swelling, need for medication (analgesics)', which is a minimum of 7 days and maximum of 3 months and OHRQoL which is minimum of 6 months and a maximum of as long as possible • Database search and hand search performed on 12/08/2021, updated on 31/10/2021
Exclusion criteria	• Animal and *In vitro* studies • Tooth type: deciduous teeth • Studies without abstracts and full texts

Abbreviations: AP, apical periodontitis; C, comparison; I, intervention; O, outcome; OHRQoL, oral health-related quality of life; P, population.

reference lists of all included papers and in previously published reviews during the last 20 years of the International Endodontic Journal and the Journal of Endodontics. Furthermore, to identify conference papers and other grey literature, additional searches were performed using Google Scholar (first 100 returns).

Publication retrieval

Two independent reviewers (NM and PJP) identified the records through the databases. The eligibility criteria for this review are mentioned in Table 1. Duplicates were removed via the EndNote™ reference manager. The titles,

abstracts and full texts were screened by both reviewers. Publications that did not meet the inclusion criteria were excluded upon reviewers' agreement.

Data extraction, quality assessment and data synthesis

The data extraction was performed by two independent reviewers (NM and PJP) by means of a pre-established and piloted spreadsheet. The following details were mentioned in the spreadsheet for each included study: name and country of the first author, year published, name of the journal, type of study design, total number of participants, age distribution, number of participants with AP, outcome measures employed, type of radiographic assessment and method of radiographic assessment. In case of incomplete or missing data, the authors of the papers were contacted for clarification. If non-agreement occurred between the reviewers, the data were not used until further clarification was available (resolved by discussing with a third reviewer). In case of studies with more than two arms and/or multiple papers reporting on the same study, only the relevant data of interest was extracted.

Critical, qualitative appraisal of the included studies was performed depending on the study type and for each main outcome. For randomized controlled clinical trials (RCTs) the second version of the Cochrane risk-of-bias tool (RoB 2) was applied.[4] This tool assesses five quality criteria after which the overall risk of bias per study is calculated: (1) the randomization process, (2) deviations from intended interventions, (3) missing outcome data, (4) measurement of the outcome and (5) selection of the reported result. For the non-randomized comparative clinical trials (NRCT), the ROBINS-I tool[5] was applied. This tool assesses seven quality criteria after which the overall risk of bias per study is calculated: (1) confounding, (2) selection of participants into the study, (3) classification of interventions, (4) deviations from intended interventions, (5) missing outcome data, (6) measurement of the outcome and (7) selection of the reported result.

Agreement between reviewers was assessed with the intraclass correlation coefficient (ICC). ICC estimates and their 95% confident intervals were calculated using SPSS statistical package version 27 (SPSS Inc) based on a 2-way mixed-effects model and absolute-agreement definition.

A meta-analysis of the main outcomes between the subgroups 'immature' and 'mature' permanent teeth was conducted if sufficient data were provided. The statistical analyses for the meta-analysis were performed using RevMan software (Review Manager (RevMan) [Computer program]) version 5.4. The risk ratio (RR) was established as measure of the effect. The pooled RR was calculated using the method of Mantel–Haenszel, as well as chi-square and I^2 tests were used to assess heterogeneity among the ORs calculated (Higgins & Thompson, 2002). An I^2 test less than 40% was considered as heterogeneity that might not be important, while I^2 test greater than 50% represented substantial heterogeneity (Higgins et al., 2003). A random effects model was carried out in the presence of heterogeneity, while a fixed effects model was performed if heterogeneity was not demonstrated. Finally, 95% confidence intervals for RR were calculated and significance level of $p < .05$ was considered. A Forest plot was used to show the OR results (Lewis & Clarke, 2001).

The overall quality of evidence for each of the main outcomes per study design was rated by using the Grades of Recommendation, Assessment, Development and Evaluation (GRADE) approach (Guyatt et al., 2011). This certainty assessment was based on four main domains (risk of bias, inconsistency, indirectness and imprecision), as well as the (absolute and relative) effect obtained by the meta-analysis. Other considerations, such as publication bias and rating the dose–response gradient, the influence of all plausible residual confounding and the magnitude of the effect, were assessed as well.

RESULTS

Literature identification

The database and hand search resulted in 365 articles, of which 19 duplicate records were removed. The flow diagram of the searches is mentioned in Figure 1, which is based on the PRISMA 2020 flow diagram for new systematic reviews (Page et al., 2021). Of a total of 346 articles, 302 were excluded post title screening (almost perfect Kappa agreement of 0.98). Post-abstract screening of 44 articles (almost perfect Kappa agreement of 0.94), 18 articles remained for full-text screening. From those, 13 articles were excluded for which the reasons are mentioned in Table 2 (Alobaid et al., 2014; Aly et al., 2019; Botero et al., 2017; Chen & Chen, 2016; El-Kateb et al., 2020; Estefan et al., 2016; Jeeruphan et al., 2012; Nagy et al., 2014; Peng et al., 2017; Pereira et al., 2020; Rizk et al., 2020; Sallam et al., 2020; Yılmaz et al., 2019). From the 5 articles that met the inclusion criteria post full-text screening, the data were extracted and included for further analysis (Tables 3 and 4, Appendix 1) (Arslan et al., 2019; Brizuela et al., 2020; Jha et al., 2019; Lin et al., 2017; Silujjai & Linsuwanont, 2017). The included studies were classified into two subgroups, depending on the root development of the teeth on which revitalization was applied (mature/immature) (Table 3 and Appendix 1).

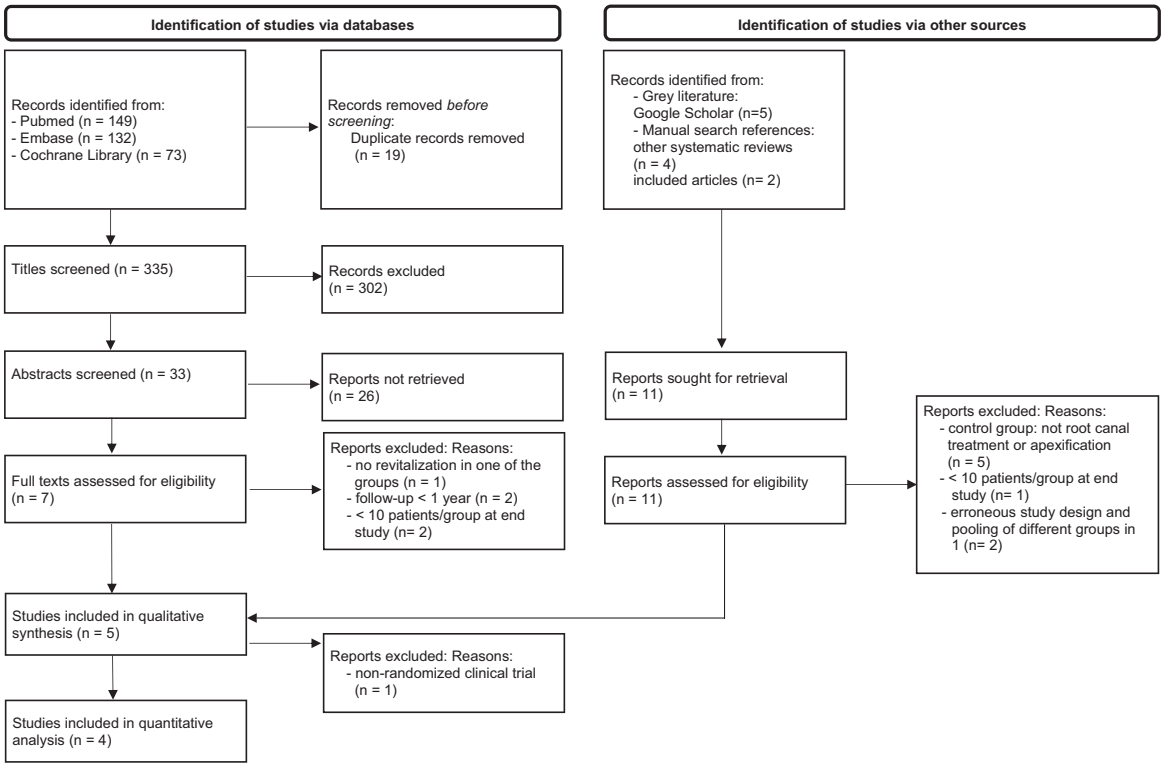

FIGURE 1 Flow diagram including searches of databases and other sources, screenings (title, abstract and full texts) and the number of included and excluded articles

TABLE 2 Excluded articles with reasons

First author, publication year	Reason for exclusion
Yilmaz, 2019	No revitalization in one of the groups
Botero, 2017	
Nagy, 2014	<10 patients/group at the end of the study
Pereira, 2020	
Peng, 2017	Control group: not root canal treatment or apexification
Rizk, 2020	
Aly, 2019	
Estefan, 2016	
El-Kateb, 2020	
Silujjai, 2017[a]	Non-randomized clinical trial
Alobaid, 2014	Erroneous study design and pooling of different groups in 1
Chen, 2016	
Sallam, 2020	Follow-up <1 year
Jeeruphan,2012	

[a]Excluded from the meta-analysis.

Assessment of heterogeneity

Study design and evaluation period

Four RCTs and one retrospective NRCT were included. One RCT was a Phase I/II study (Brizuela et al., 2020). The follow-up periods varied between 3 months and 5 years. Three studies analysed the subject at 12 months (Arslan et al., 2019; Brizuela et al., 2020; Lin et al., 2017), in two other studies the final analysis was performed at 18 months and later (Jha et al., 2019; Silujjai & Linsuwanont, 2017). The dropout rate ranged between 0% and 43% (Table 3 and Appendix 1).

Subject characteristics

Two out of five studies did not report whether male or female patients were included (Jha et al., 2019; Lin et al., 2017). In two studies the age range varied considerably (Brizuela et al., 2020; Silujjai & Linsuwanont, 2017) even if in one study (age range: 8–46 years) immature permanent teeth were treated (Silujjai & Linsuwanont, 2017). In three studies mature permanent teeth with a periapical index (PAI) score of at least 2–3 were treated (Orstavik et al., 1986); however, in Jha et al. (2019) the type of teeth (incisor/[pre]molar) was not specified (Arslan et al., 2019; Brizuela et al., 2020; Jha et al., 2019). In these studies, revitalization was compared with conventional root canal treatment (CRCT). In the two other included studies nonvital, immature permanent teeth were treated and in one of those the type of tooth was not specified (Lin et al., 2017; Silujjai & Linsuwanont, 2017). Only in these

TABLE 3 Data extraction of the included articles

First author, year published	Arslan H, 2019	Brizuela C, 2020	Jha P, 2019	Lin J, 2017	Silujjai J, 2017
Study design	RCT	RCT Phase I/II	RCT	Prospective RCT	Retrospective NRCT
Age range	18–30 y	16–58 y	9–15 y	8–16 y	8–46 y
Follow-up	12 m	6, 12 m	6, 12, 18 m	3, 6, 9, 12 m	6 m, 1–5 y
Groups (*n*)	rev ($n = 26$) CRCT ($n = 20$)	rev + PPP-UC-MSCs ($n = 18$) CRCT ($n = 18$)	SealBio rev ($n = 15$) CRCT ($n = 15$)	rev ($n = 69$) MTA apex ($n = 34$)	rev ($n = 17$) MTA apex ($n = 26$)
Patient dropout	14%: 56 included, 8 dropout (2 rev, 8 CRCT)	0%	0%	13%: 118 included, 15 dropout (11 rev, 4 MTA apex)	42.7%: 75 eligible, 46 contacted, 43 attended recall
Results main outcome(s) at final follow-up	Success: ($p > .05$) rev: 92.3% CRCT: 80%	Survival: all analysed teeth	Success: ($p = .62$) SealBio rev: 13 healed, 2 healing CRCT: 12 healed, 3 healing	Success and survival: all analysed teeth 100%	*Success: ($p > .05$) rev 76.47% MTA apex 80.77% *Survival: ($p > .05$) rev: 88.24% MTA apex: 82.76%

Note: All included teeth had apical periodontitis. Colour indication for subgroups: white: mature teeth, blue: immature teeth.

Abbreviations: CRCT, conventional root canal treatment; DE, dens evaginatus; m, months; MTA apex, mineral trioxide aggregate apexification; *n*, number of teeth; (N)RCT, (non-)randomized controlled clinical trial; PPP-UC-MSCs, platelet poor plasma – umbilical cord mesenchymal stem cells; rev, revitalization; y, year.

two studies, comparing revitalization to mineral trioxide aggregate (MTA) apexification, the etiological reason for AP was mentioned (caries, trauma, or dens evaginatus).

Treatment protocols

In Brizuela et al. (2020), a combination of the cell homing and cell-based concept was applied in revitalization, more specifically: after triggering a blood clot periapically (= cell homing), allogenic umbilical cord mesenchymal stem cells encapsulated in plasma-derived biomaterial were transplanted into teeth (= cell-based) (Diogenes et al., 2013; Lin et al., 2021). This revitalization treatment concept was quite different from that of the four other included studies, as these studies relied on the recruitment of only endogenous mesenchymal stem cells for revitalization by triggering a blood clot periapically (= cell homing). Hence, the pool of mesenchymal stem cells for the revitalized mature teeth in Brizuela et al. (2020) was greater than that for Arslan et al. (2019) and Jha et al. (2019).

Regarding the irrigation protocols, the sodium hypochlorite (NaOCl) and ethylenediaminetetraacetic acid (EDTA) concentrations applied were similar in both groups per study and amounted 1%–2.5% and 17% respectively (Table 2). In Arslan et al. (2019) distilled water was additionally applied in the second revitalization session and in Lin et al. (2017) in both revitalization sessions 0.9% saline was applied. To activate the disinfectant, in Brizuela et al. (2020) the Endoactivator system (Dentsply Tulsa Dental Specialties) was used and in Jha et al. (2019) negative pressure.

Regarding the number of treatment sessions, in CRCT it was not reported or performed in two sessions with 1–3 weeks in between. For MTA apexification this was not mentioned or performed in three sessions with one-week intervals. Revitalization was performed in two to three sessions with 1–3 week intervals. As intermediate root canal dressing for the comparator, mostly calcium hydroxide was used. A tri-antibiotic paste, combining metronidazole and ciprofloxacin with minocycline/doxycycline/clindamycin, was applied as an intracanal medication in all revitalization groups.

As root canal filling, warm gutta percha was applied upon the MTA-plug in the MTA-apexification groups and gutta percha and sealer in the CRCT groups. In the revitalization groups, a blood clot was triggered in all studies, and in one study platelet poor plasma with umbilical cord mesenchymal stem cells were added to this blood clot (Brizuela et al., 2020). In two studies a resorbable collagen sponge was placed upon the blood clot (Brizuela et al., 2020; Lin et al., 2017). MTA was applied as seal upon the blood clot in three studies, Biodentine (Septodont) in one study, and in another study no calcium silicate cement was applied (Jha et al., 2019). The coronal restoration was in four studies composite resin and not specified in one study (Jha et al., 2019).

Assessment methods

Regarding the radiographic assessment, in all studies the radiographic follow-up was performed by means of

TABLE 4 (a) Risk of bias summary: review authors' judgements about each risk of bias item for each included randomized controlled clinical trial per main outcome (success and survival). (b) Risk of bias summary: review authors' judgements about each risk of bias items for 1 included non-randomized comparative trial per main outcome (success and survival)

(a)

Aim	Ouctome	Study	Randomization	Deviation from intervention	Missing data	Measurement of outcome	Selection of reported results	Overall
Intention-to-treat	Success	Arslan et al. (2019)	!	-	+	+	-	-
		Lin et al. (2017)	-	-	-	-	!	-
		Jha et al. (2019)	-	!	+	+	!	-
	Survival	Lin et al. (2017)	-	-	-	+	!	-
		Brizuela et al. (2020)	+	+	+	+	+	+

(b)

Study	Ouctome	Confounding	Selection	Intervention classification	Deviation from intervention	Missing data	Measurement of outcome	Selection of reported results	Overall
Silujjai and Linsuwanont (2017)	Success	-	+	-	+	-	!	!	-
	Survival	-	!	-	+	-	!	+	-

Note: Dots: green = low risk, yellow = some concerns, red = high risk.

periapical radiographs (PR). However, in two studies cone beam computed tomography (CBCT) was applied additionally (Brizuela et al., 2020; Lin et al., 2017). In two out of five studies the positioning of the periapical radiographs was standardized (Arslan et al., 2019; Lin et al., 2017). In four studies a qualitative scoring system was used for the assessment of the periapical lesion (Arslan et al., 2019; Brizuela et al., 2020; Estrela et al., 2008; Jha et al., 2019; Lin et al., 2017; Orstavik et al., 1986). Only in one study the periapical lesion was quantitatively measured with CBCT (Brizuela et al., 2020). The two studies assessing further root development of immature permanent teeth were heterogenous in the device applied (CBCT versus PR) and the assessment method (Appendix 1) (Lin et al., 2017; Silujjai & Linsuwanont, 2017).

Regarding the clinical assessments, clinical signs and adverse events were generally reported in all trials (Appendix 1). However, only one trial adequately measured the OHRQoL and pain symptoms (Arslan et al., 2019) and two studies assessed the pulp sensitivity (Arslan et al., 2019; Brizuela et al., 2020).

Study outcomes

The *most critical outcome 'survival'* was not reported by one study (Arslan et al., 2019). However, in 75% of the included studies that did report survival, it was considered as the main outcome (Brizuela et al., 2020; Lin et al., 2017; Silujjai & Linsuwanont, 2017) (Table 3). In three studies the survival rate at 12 months was 100% for all permanent teeth in all groups, independent of the tooth type (mature/immature) or treatment modality (revitalization, CRCT or MTA apexification) (Brizuela et al., 2020; Jha et al., 2019; Lin et al., 2017).

Regarding the *critical outcomes* of this review, a combination of clinical symptoms ('pain, tenderness, swelling') and radiographic findings ('radiographic evidence of reduction in apical lesion size' and 'radiographic evidence of increased root thickness and length' (not for mature teeth)) were defined as *success*, which was the main outcome in 80% of the studies (Arslan et al., 2019; Jha et al., 2019; Lin et al., 2017; Silujjai & Linsuwanont, 2017) (Table 3 and Appendix 1). In immature teeth, Lin et al. (2017) reported a significant difference in root lengthening and thickening at 12 months in favour of the revitalized group in comparison with the MTA-apexification group and independent of the ethiology (Lin et al., 2017). Nevertheless, in Silujjai and Linsuwanont (2017) this was not the case for root lengthening and dens evaginatus cases presented the most increase in root development in comparison with trauma and dental caries cases (Silujjai & Linsuwanont, 2017) (Appendix 1).

In Lin et al. (2017) the 12 months success rate for immature teeth amounted 100% in the revitalization as well as in the MTA apexification group. Nevertheless, in Arslan et al. (2019), mature teeth undergoing revitalization were more successful (92%) than the teeth in the CRCT group (80%) at 12 months, but this was statistically insignificant ($p > .05$).

Other critical outcomes such as 'radiographic evidence of normal periodontal ligament space' and 'need for medication (analgesics, antibiotics)' were in 60–100% of the studies respectively not reported (Appendix 1).

Regarding the *additional outcomes* of the current review, as mentioned above 'OHRQoL' and 'response to sensibility testing' were rarely assessed. However, the other additional outcomes mentioned in Table 1 were reported in all included studies (but not as main outcome) (Appendix 1).

Funding

Only in one trial the funding resources were not mentioned (Silujjai & Linsuwanont, 2017). Two studies did not use any funding and two other trials received institutional or government grants (Appendix 1).

Quality assessment

The results of the qualitative assessment of the four included RCTs are mentioned in Table 4a. For the most critical outcome 'survival' this assessment resulted in a high risk of bias for one study (Lin et al., 2017) and in a low risk of bias for another (Brizuela et al., 2020). For the critical outcome 'success' three studies were highly biased (Arslan et al., 2019; Jha et al., 2019; Lin et al., 2017). Independent of the outcome criteria, mostly the thresholds 'randomization', 'deviations from intended interventions' and 'selection of reported results' showed methodological limitations (Figure 2a,b).

The only NRCT was assessed with the ROBINS-I tool (Table 4b). This study was highly biased for both survival and success (Silujjai & Linsuwanont, 2017).

The qualitative assessments were performed with good inter-rater reliability for success (ICC = 0.86, 95% CI [0.66; 0.95) and perfect agreement for survival (ICC = 1).

Quantitative analysis

The subgroups (mature/immature permanent teeth) of the RCTs were subjected to quantitative analysis to compare the survival and success rates of revitalization with CRCT or MTA apexification.

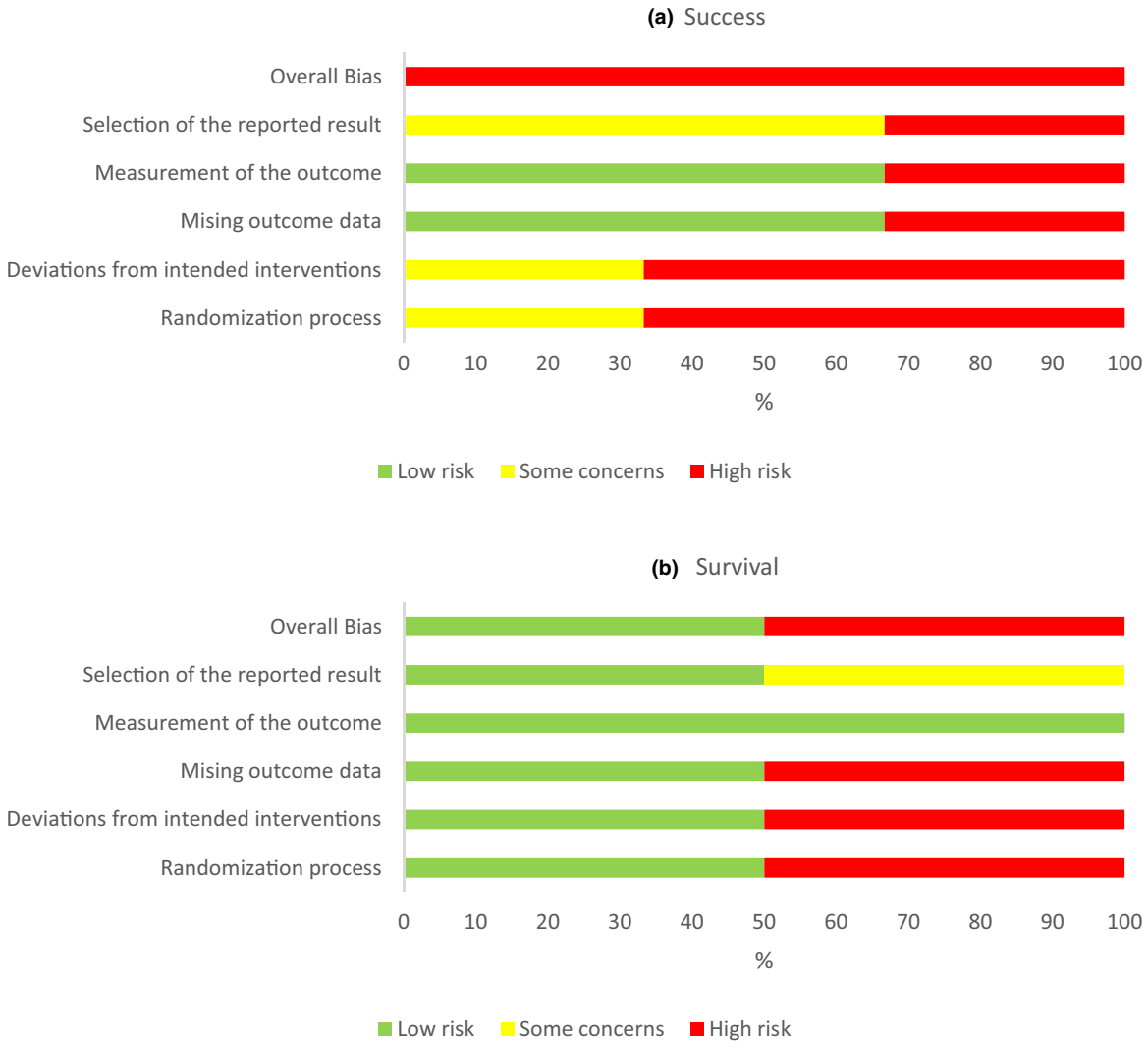

FIGURE 2 Summary of risk of bias assessments (based on Table 4a) for quality criteria per main outcome (success or survival)

Survival

For each included RCT that reported survival rate data at 12 months (or later), results were extracted, classified into mature (Brizuela et al., 2020; Jha et al., 2019) or immature (Lin et al., 2017) permanent tooth subgroup, and RRs were calculated. The analysis of pooled heterogeneity and variance between the studies was non-significant ($Chi^2 = 0.00$; df = 2; $p = 1.00$; $I^2 = 0$), indicating homogeneity between the RRs of the included studies. The Mantel–Haenszel method with fixed effects provided a pooled RR = 1.00 (95% CI = 0.96–1.04; $p = 1.00$), indicating non-statistically significant differences between the survival of revitalization group versus the CRCT or MTA apexification group. Results without statistically significant differences were also found within the subgroup of mature (RR = 1.00; 95% CI = 0.92–1.08; $p = 1.00$) and immature teeth (RR = 1.00; 95% CI = 0.96–1.05; $p = 1.00$). Forest plot shows the RRs for each study and the RRs for both subgroups and overall calculated from the meta-analysis (Figure 3).

Success

To analyse the success of the treatment, the results of each included article that reported success rate data at 12 months were extracted, being classified according to the subgroup of mature teeth (Arslan et al., 2019) or immature (Lin et al., 2017), and the RRs were calculated. The analysis of variance between the studies was significant ($Tau^2 = 0.03$; $Chi^2 = 4.14$; df = 1; $p = .04$) and the I^2 test (=76%) showed substantial heterogeneity between the RRs of the included studies. Mantel–Haenszel method with random effects provided a pooled RR = 1.06 (95% CI = 0.83–1.35; $p = .66$), indicating a slight favour, but without statistically significant differences, in the success of the revitalization treatment with respect to the CRCT or

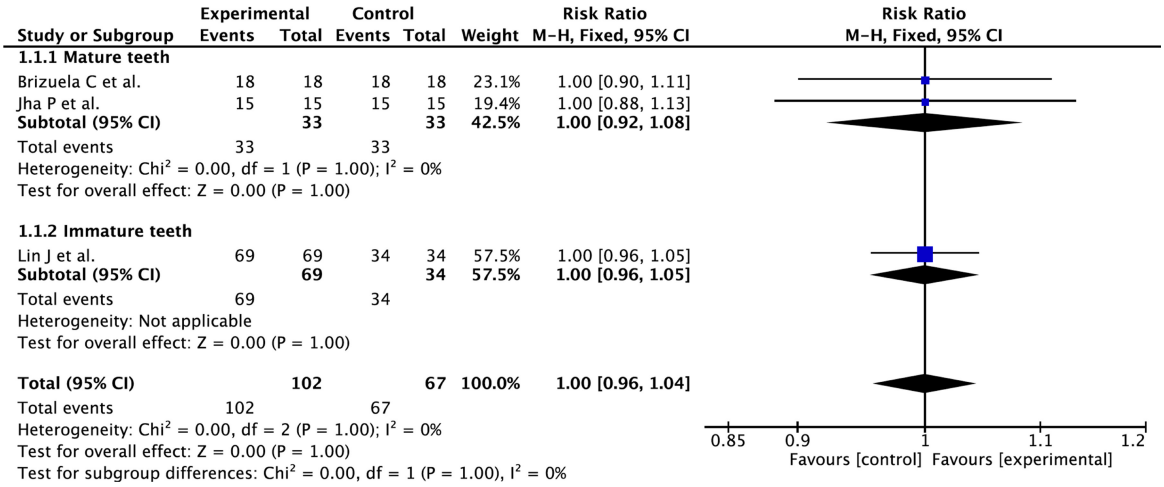

FIGURE 3 Forest plot of subgroup analysis of survival rates

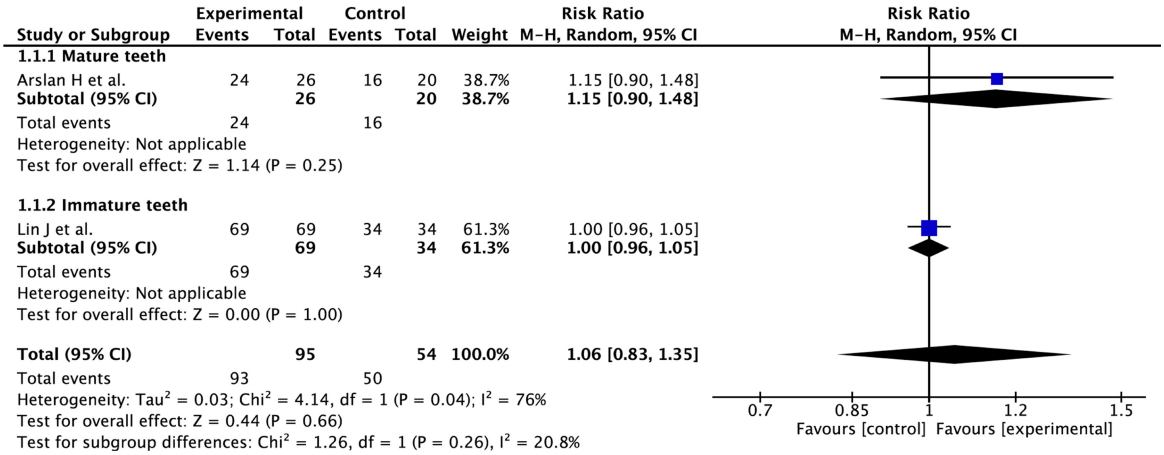

FIGURE 4 Forest plot of subgroup analysis of success rates

MTA apexification treatment. Results without statistically significant differences were also found within the treatment of mature (RR = 1.15; 95% CI = 0.90–1.48; $p = .25$) and immature teeth (RR = 1.00; 95% CI = 0.96–1.05; $p = 1.00$). Forest plot shows the RRs for each study and the RRs for both subgroups and overall calculated from the meta-analysis for the success outcome (Figure 4).

Certainty assessment

The overall quality of the evidence of each main outcome has been rated for the RCTs in the Summary of Findings (SoF) Table (Table 5). Non-randomized studies on intervention effects, such as Silujjai and Linsuwanont (2017), can be assessed for certainty by means of the ROBINS-I tool. The same downgraders (risk of bias, inconsistency, indirectness, imprecision and publication bias) and upgraders (dose–response gradient, plausible residual confounding and effect magnitude) as for RCTs are used in GRADE. However, for NRCT the level of evidence can be downgraded up to 3 levels in comparison with RCTs (up to 2 levels). Nevertheless, no GRADE assessment was performed for Silujjai and Linsuwanont (2017), as it was the only NRCT of this review, highly biased and excluded from the meta-analysis (Table 2). Hence, this study would have no added value to clinical decision making.

Regarding the critical outcome 'success' of the two RCTs assessed, the level of evidence has been downgraded with one level to 'very low' due to inconsistency and imprecision. Regarding the most critical outcome 'survival', the level of evidence was kept 'low'. Nevertheless, also for this outcome, imprecision due to a small number of events was scored as 'serious' (Table 5).

DISCUSSION

Revitalization is a biologically based endodontic treatment with promising pre-clinical results, aiming to preserve or

TABLE 5 Summary of findings table from the GRADEpro Guideline Development Tool (https://gradepro.org)

Certainty assessment							No. of patients		Effect			
No. of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Revitalization**	**Calcium hydroxide apexification, apical plug and root canal treatment**	**Relative (95% CI)**	**Absolute (95% CI)**	**Certainty**	**Importance**
Clinical and radiographic success—follow-up at 12 months												
2[a]	Randomized trials	Serious[b]	Serious[c]	Not serious	Serious[d]	None	93/95 (97.9%)	50/54 (92.6%)	RR 1.06 (0.83 to 1.35)	56 more per 1000 (from 157 fewer to 324 more)	⨁◯◯◯ Very low	Critical
Survival—follow-up at 12 months												
3[e]	Randomized trials	Serious[f]	Not serious[g]	Not serious	Serious[d]	None	102/102 (100.0%)	67/67 (100.0%)	RR 1.00 (0.96 to 1.04)	0 fewer per 1000 (from 40 fewer to 40 more)	⨁⨁◯◯ Low	Most critical

Abbreviations: CI, confidence interval; RR, risk ratio.

[a]Arslan et al. (2019) and Lin et al. (2017). Jha et al. (2019) was not included in this table as the results for success at 12 months were not mentioned in this study. Results for success at 18 months cannot be extrapolated to 12 months.

[b]See Table 4a.

[c]Figure 4: CIs have reasonable overlap. Substantial statistical heterogeneity: $p = .04$, $I^2 = 76\%$. Therefore, inconsistency was downgraded by one level.

[d]<400 events = few events and hence not enough power to obtain a reliable level of certainty.

[e]Brizuela et al. (2020), Jha et al. (2019) and Lin et al. (2017). Survival was not the main outcome in Jha et al. (2019), nevertheless this outcome was assessed in this study at 18 months (which can be extrapolated to 12 months).

[f]See Table 4a: based on Brizuela et al. and Lin et al. (2017).

[g]Figure 3: CIs have a perfect overlap. No heterogeneity, but statistically insignificant: $p = 1$, $I^2 = 0\%$.

regain as much as possible the entity and functionality of the pulp–dentine complex. The primary goal of revitalization procedures is to eliminate clinical symptoms and heal periapical lesions (Galler et al., 2016). Consequently, it is important to verify if this goal has clinically been reached.

Strengths

Via a systematic approach, the literature has been reviewed to assess the efficacy of revitalization in treating AP. This approach is of utmost importance to obtain a full and impartial view of what has been published so far. The carefully selected and consensus-based outcome measures (Duncan et al., 2021), narrow focus or PICO question (Table 1), comprehensive search for evidence based on a pre-established protocol (Figure 1), criterion-based selection of evidence (Table 4a,b), thorough qualitative and quantitative appraisal of validity (Table 5; Figures 3 and 4) and evidence-based conclusions form the strengths of this review. Nevertheless, numerous critical concerns arose during this process that may be considered as limitations. Hence, contradictorily, the ultimate strength of the current review lies in its limitations (described below), which might offer new perspectives for further research in revitalization procedures.

Remarkably, 80% of the included articles seem not to have a conflict of interest or partiality based on funding resources (Appendix 1).

Limitations

Methodological concerns

Only a few articles met the eligibility criteria (Figure 1). In all included articles, revitalization seems to be effective to treat AP in terms of clinical and radiographic success and survival in (im)mature permanent teeth in comparison with CRCT or MTA apexification (Table 3). Nevertheless, 90% of the articles were highly biased (Table 4a,b and Figure 2) and even more downgraded due to mainly inconsistency and imprecision concerns (Table 5). Furthermore, publication bias could not be analysed due to the lack of existing published studies, which may result in a systematic overestimation of treatment benefit.

Mature versus immature teeth

Initially, revitalization procedures were rather recommended to treat immature permanent teeth with inflamed or necrotic pulp to prevent discontinued maturogenesis (Galler et al., 2016). Nevertheless, ever since, gradually more trials have implemented this treatment in mature permanent teeth (Scelza et al., 2021). Furthermore, in Silujjai and Linsuwanont (2017) revitalization was performed on permanent teeth with open apices in patients up to 46 years old. Besides the fact that these studies are experimental and the long-term prognosis of these teeth is unknown, it is unlikely that further root development (in case of immature teeth) will take place at an older age as the pool of mesenchymal stem cells depletes with age (Hilkens et al., 2015). Additionally, none of the mesenchymal stem cells could induce further root development if the Hertwig's epithelial root sheath has broken down into the epithelial cell rests of Malassez (Tucker & Sharpe, 2004). Hence, the pool of mesenchymal stem cells for the cell-based revitalized mature permanent teeth in Brizuela et al. (2020) was greater than that for the cell homing based studies Arslan et al. (2019) and Jha et al. (2019). Nevertheless, this did not impact the outcomes (Appendix 1) nor the quantitative analysis of the two most comparable studies, Jha et al. (2019) and Brizuela et al. (2020). Furthermore, in case of mature permanent teeth, the long-term survival of the coronal restoration in severely restored revitalized teeth should be investigated.

Clinical and radiographic assessment

One of the goals in revitalization is to maintain or regain the pulpal sensibility (Galler et al., 2016). Nevertheless, in only 40% of the included trials this is tested (Appendix 1) and in one study the reliability of this test is doubtable. More specifically, in Brizuela et al. (2020), mature permanent teeth post CRCT have been tested for sensibility.

Regarding adverse events, MTA discolouration was mostly reported in cases where MTA was applied as calcium silicate cement (CSC) in revitalization (Appendix 1). This is mainly due to leakage of the radio-opacifier bismuth oxide (Palma et al., 2019a; Palma et al., 2020). As in revitalization the CSCs are applied coronally, in future treatment guidelines it is preferable that CSC without bismuth oxide or other discolouring agents are recommended.

Regarding the radiographic assessment of revitalized teeth, the assessment device and method are of utmost importance for reliable outcome determination. Follow-up with PR is recommended by the ESE position statement on revitalization procedures and has been applied the most in clinical trials (Galler et al., 2016; Torabinejad et al., 2017). Nevertheless, interpretation of PRs is influenced by the image quality and angulation. Positioning tools (stents e.g.) to standardize and algorithms to adjust

the angulation of PRs might reduce this problem (Bose et al., 2009). Nevertheless, young patients outgrow individualized positioning tools during a long follow-up period (Meschi et al., 2021) and adjusting software might occasionally lead to image distortion and elongation (Silujjai & Linsuwanont, 2017). Furthermore, it has been described that the accuracy of PRs is much less than that of CBCT (Ezeldeen et al., 2015; Meschi et al., 2018; Meschi et al., 2021). Hence, especially in multidisciplinary decision making in young patients with revitalized teeth with uncertain prognosis, an optimized (low dose) CBCT should be recommended to prevent long-term orthodontic and aesthetic problems (Ezeldeen et al., 2017; Meschi et al., 2019).

Meta-analysis

Only three studies for survival and two studies for success met the criteria to be included in the quantitative analysis. Although survival data were reported for 168 treatments and 143 for success, the statistical power of the meta-analysis is limited, and the results should be interpreted with caution, with further studies needed to improve the strength of the combination.

CONCLUSIONS

The success and survival rates of revitalized and fully pulpectomized (im)mature permanent teeth did not differ significantly. However, the sparse and low-quality evidence discovered cannot form a solid basis to support the statement that revitalization is effective to treat AP in (im)mature permanent teeth. Meticulously performed, high-quality clinical trials are urgently necessary to increase the clinical credibility in revitalization of the pulp–dentine complex. Hence, clinicians should be cautious with the application of this endodontic treatment modality. Until reliable evidence is available, revitalization should only be performed in well indicated cases, with the consent of the patients (and their guardian) and must be seen as a last resort to preserve dentoalveloar tissues.

AUTHOR CONTRIBUTIONS

Nastaran Meschi contributed to PICOTS, PROSPERO Protocol, literature search, title/abstract/full-text screening, data extraction, qualitative analysis, guidance meta-analysis, SoF-table, tables and figures, writing (except for meta-analysis and statistics), revisions and corresponding author. Paulo Palma contributed to literature search, title/abstract/full-text screening, data extraction, qualitative analysis, statistics qualitative analysis and revisions. Daniel Cabanillas-Balsera contributed to PICOTS and meta-analysis.

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CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

DATA AVAILABILITY STATEMENT

Data sharing not applicable - no new data generated

ETHICAL STATEMENT

This study did not require ethical approval.

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ENDNOTES

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[5] https://methods.cochrane.org/methods-cochrane/robins-i-tool [accessed on 30 September 2021].

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APPENDIX 1
DATA EXTRACTION OF THE INCLUDED ARTICLES

AB, antibiotic; AP, apical periodontitis; apex, apexification; BC, blood clot; CBCT PAI, cone beam computed

tomography periapical index (Estrela et al., 2008); CBCT, cone beam computed tomography; CEJ, cementoenamel junction; CH, calcium hydroxide; CHX, chlorhexidine; CRCT, conventional root canal treatment; CSC, calcium silicate cement; d, days; DE, dens evaginatus; EDTA, ethylene diamine tetra acetic acid; GP, gutta percha; m, months; M/F, male/female; MTA, mineral trioxide aggregate; *n*, number; n.a., not applicable; NaCl, saline; NaOCl, sodium hypochlorite; NSRCT, non-surgical root canal treatment; OHRQoL, oral health-related; PAI, periapical index (Orstavik et al., 1986); PPP-UC-MSCs, platelet poor plasma - umbilical cord mesenchymal stem cells; PR, periapical radiograph; quality of life; RCT, randomized controlled clinical trial; REP, regenerative endodontic procedure; revasc, revascularization; RRA, radiographic root area; VAS, visual analogue scale; w, weeks; WL, working length; y, year.

First author, country	**Arslan H, Turkey**	**Brizuela C, Chile**	**Jha P, India**	**Lin J, China**	**Silujjai J, Thailand**
Year published	2019	2020	2019	2017	2017
Journal name	Journal of Endodontics	Journal of Dental Research	International Journal of Clinical Paediatric Dentistry	Journal of Endodontics	Journal of Endodontics
Study design	RCT	RCT Phase I/II	RCT	Prospective RCT	Retrospective, comparative, non-randomized study
Age range	18–30 y	16–58 y	9–15 y	8–16 y	8–46 y
M/F	35 M/11F	11 M/25F	not reported	not reported	19 M/24F
Teeth type and maturity	Nonvital, mature, single-rooted teeth (anterior, premolar), PAI score ≥3	Maxillary or mandibular incisors/canines and mandibular premolars, mature apex, pulp necrosis and periapical lesion (PAI score ≥2 and CBCTPAI ≥1)	Mature, infected permanent teeth with AP (PAI score ≥3)	Immature teeth (premolar, central incisor) with 1 root canal, open apices larger than 1 mm, periapical lesion	Cvek stage 2–4 immature, nonvital, permanent teeth
Follow-up	12 m	6, 12 m	6, 12, 18 m	3, 6, 9, 12 m	6 m, 1–5 y
n with AP	All included	All included	All included	All included	All included
Aetiology	Not mentioned	Not specifically mentioned, but not dens invaginatus and not avulsion	Not reported	DE (all premolars), trauma (all incisors)	Trauma, caries, DE
Groups and *n*/group	Test: REP (28 included, 26 analysed) Control: CRCT (28 included, 20 analysed)	Test: REP + PPP-UC-MSCs ($n = 18$) Control: CRCT ($n = 18$)	Test: SealBio ($n = 15$) Control: NSRCT ($n = 15$)	Two main groups (REP and MTA apex) with 2 subdivisions (aetiology/type of tooth): • Test: REP ($n = 69$; 21 central incisors/trauma, 48 premolars/DE) • Control: MTA apex ($n = 34$; 13 central incisors/trauma, 21 premolars/DE)	Test: revasc ($n = 17$; 5 trauma, 10 DE, 2 caries) Control: MTA apex ($n = 26$; 15 trauma, 8 DE, 3 caries)
Patient dropout (% of recall)	14%	None	None	118 included, 15 (=13%) dropout (lost/quit): 11 REP (5 DE, 6 trauma), 4 MTA apex (2 DE, 2 trauma)	75 eligible, 46 contacted, 43 attended recalls (patient recall rate = 57.33%)

First author, country	Arslan H, Turkey	Brizuela C, Chile	Jha P, India	Lin J, China	Silujjai J, Thailand
Irrigant	CRCT: first visit: 7 ml NaOCl 1%, 5 min. EDTA 17%; second visit: 5 min. EDTA 17%, 5 ml saline. REP: first visit: 7 ml NaOCl 1%, 5 min. EDTA 17%; second visit: distilled water, 5 ml NaOCl 1% for 1 min., 2 ml 5% EDTA for 1 min., 5 ml distilled water	20 ml 2.5% NaOCl and Endoactivator system (Dentsply Tulsa Dental Specialties), 20 ml 17% EDTA	SealBio: first session: negative pressure irrigation (Endovac, Discus dental) with 2.5% NaOCl, second session: 17% EDTA; – NSRCT: negative pressure irrigation with 2.5% NaOCl	REP: first session: 20 ml 1.5% sodium hypochlorite, 0.9% saline, and 20 ml 17% EDTA; second session: 0.9% saline, and 20 ml 17% EDTA MTA apex: 20 ml 1.5% sodium hypochlorite solution 0.9% physiological saline, and 20 ml 17% EDTA; second session: 17% EDTA	Revasc: first: 1.5%–2.5% NaOCl, 17% EDTA; 2nd visit: not mentioned; Apex: 2.5% NaOCl
Intracanal medication	CRCT: CH REP: AB 3mix [doxycycline, metronidazole, ciprofloxacin]	CH	SealBio: AB 3mix (3MixMP: minocyclin, metronidazole, ciprofloxacin)	REP: 0.1 mg/ml AB 3mix [ciprofloxacin, metronidazole, clindamycin; 1:1:1 mixed with distilled water] MTA apex: CH, after 1 w Vitapex paste (Neo Dental International, Inc) until apical barrier formation radiographically confirmed	Revasc: CH or AB 3mix [1:1:1 ciprofloxacin 250 mg, metronidazole 400 mg, and minocycline 50 mg] Apex: CH
Number of visits and time between	CRCT: 2, 1w REP: 3, 3w and 1d respectively	2, 3 w	SealBio: 2, 1–2 w NSRCT: not specified	REP: 2, 3w MTA apex: 3, 1w between 2 first sessions	2, time between not mentioned
Root canal filling	CRCT: gutta-percha cones and epoxy resin sealer (2Seal; VDW) REP: blood clot and MTA	CRCT: gutta-percha cones (Reciproc® VDW, GmbH) and Topseal® sealer (Dentsply Sirona) REP: blood clot, PPP-UC-MSCs and an absorbable gelatin sponge hemostats (Gelita-Spon® GmbH)	SealBio: blood clot+ calcium sulfate-based cement (Cavit G) into the cervical 1/3 root NSRCT: conventional cold lateral condensation technique (no further specifications)	REP: blood clot+ absorbable collagen barrier (Heal-all Biological Membrane; Zhenghai Biological Technology) MTA apex: warm gutta percha	Apex: injectable gutta-percha (Obtura II; Obtura Spartan, Fenton, MO) and AH Plus sealer (Dentsply DeTrey) Revasc: blood clot and MTA
CSC (type/size)	REP: white MTA, 3 mm intra-radicular until CEJ (Cerkamed MTA; Wojciech)	REP: Biodentine™ (Septodont)	Not applied	REP: white ProRoot MTA (Dentsply International, Inc)	REP: MTA (brand not specified; 2–3 mm); Apex: MTA-plug (brand and size not specified)
Coronal restoration	Composite resin	Composite resin	Not specified	Composite resin	Composite filling/crown

First author, country	Arslan H, Turkey	Brizuela C, Chile	Jha P, India	Lin J, China	Silujjai J, Thailand
Type of RX	PR	PR and CBCT	PR	PR and limited field of view CBCT (PHT-6500; Vatech Co, Ltd, Gyeonggi-do, Korea [90 kV and 7.0 mA])	PR
RX assessment method	Standardization of pre- and post-op PR, Image J (Version 1.41; National Institutes of Health, Bethesda, MD): to measure the change of lesion size pre-post +4 scores: absence (=1)/reduction (=2)/enlargement (=3) of periapical lesion/uncertain (=4)	Not reported	Pre- and postoperative RX: bite registration as a positioning index, same exposure settings PAI-scores = qualitative assessment of AP, measured by 3 blinded assessors.	Qualitative: PR: periapical radiolucency Quantitative: CBCT: root length: average of distance CEJ - apical endpoint measured distally and mesially; root thickness: average of values measured at 4, 6, and 8 mm from the CEJ at the distal, mesial, buccal, and lingual positions; apical foramen: averaged from values of the buccolingual and mesiodistal positions, in apexification cases, the apical foramen size was recorded as 0 if the apical barrier formed.	Root length and dentin thickness: measured on preoperative and follow-up PR using the straight-line tool in ImageJ software; Root length: straight line from the CEJ to the radiographic apex; Dentinal wall thickness: at the apical one third of the preoperative root length measured from the CEJ.

First author, country	Arslan H, Turkey	Brizuela C, Chile	Jha P, India	Lin J, China	Silujjai J, Thailand
Main outcome(s)	Clinical and radiographic success/failure: RX score 1 or 2 and clinically asymptomatic = successful RX score 3 or 4 and or clinically symptomatic = unsuccessful	Safety and efficacy:—*safety* = root fracture, severe or moderate pain, and extra/intraoral inflammation—*efficacy* = tooth survival, no percussion pain, an apical bone lesion of equal size in the 3 dimensions of space, a decrease in some of them, or no more than a 0.1-mm increase in one of them (PR and CBCT).	Primary: change in apical bone density during follow-up (by means of PAI)—secondary: clinical signs and symptoms during follow-up—final outcome = primary + secondary at 18 m: Healed: combined radiographic and clinical normalcy Healing: reducing radiolucency with clinical normalcy Diseased: if the radiolucency persisted without change with/without clinical normalcy	Survival, clinical and radiographic success/failure: *Success* = elimination of symptoms, disappearance of apical radiolucency with an increase of root length or a decrease of the apical foramen, or both. *Failure* = if 1 of the following was present: presence of clinical symptoms (pain, swelling, or sinus tract), no change in root length or apical size, recurrence of apical periodontitis, and external root resorption.	Clinical and radiographic success/failure, and functional retention: *Success*: clinical and radiographic presentations were normal or showed reduced radiolucency combined with normal clinical presentation; *Failure:* radiolucency that emerged or persisted without change, even when the clinical presentation was normal, or patients' clinical signs or symptoms were present, even if the radiographic presentation was normal; *Functional retention:* clinical presentation was normal, whereas radiolucency may have been absent or present (newly emerged or persisting).
Additional outcome(s)	REP: positive response to vitality testing (Digitest ii; Parkell)	Changes in cortical bone Pulpal response: sensitivity and vitality test	Timing treatments: recorded after the teeth were anaesthetized and isolated using a rubber dam till the completion of the SealBio procedure before placing the coronal restoration and till the completion of the obturation procedure before placing the coronal restoration for NSRCT	Impact of aetiology on the outcome of REP and MTA apex Discolouration and calcification in REP	Root canal wall thickening and lenghtening
Pain pre/post	VAS: - CRCT: pre: 36.95 ± 35.07, 7d post: 0 REP: pre: 44.15 ± 27.25, 7d post: 0	Pre: not reported Post: none	Pre: not reported Post: none	Pre: not reported Post: none (100% asymptomatic)	Not specifically reported

First author, country	Arslan H, Turkey	Brizuela C, Chile	Jha P, India	Lin J, China	Silujjai J, Thailand
Tenderness pre/post	CRCT: pre: 30%, 7 d post: 0; REP: pre: 50%, 7 d post: 0	Pre: not reported Post: REP: at 6 m, 1 individual (5.6%)	Pre: not reported Post: none	Pre: not reported Post: none (100% asymptomatic)	Not specifically reported
Swelling pre/post	CRCT: pre: 40%, post: 0 REP: pre: 46.2%, post: 3.8%	Pre: not reported Post: none	Pre: not reported Post: none	Pre: not reported Post: none (100% asymptomatic)	Not specifically reported, in case of acute apical abscess: pre: 2 MTA apex, 1 revasc
Need for medication pre/post[a]	Not reported	Not reported	Not reported	Pre/post: not specifically reported	Not reported
Radiographic evidence of increased root thickness and length	Not measured	Not measured	Not measured	Size of apical foramen, root length and thickness: *REP and MTA apex*: pre-op: no significant difference ($p > .05$); at 12 m: statistical difference for all these parameters ($p < .05$) in favour of REP group (increase root length: REP 81.16%, MTA apex 26.47%; increase root thickness: REP 82.60%, MTA apex 0%; apex closure: REP 65.21%, MTA apex 82.35%) *DE and trauma at 12 m*: DE: statistical difference for root length and thickness ($p < .001$) in favour of REP group; trauma: increase in root thickness significant difference in favour of REP ($p < .05$)	Root width: revasc: 13.75% ± 19.91%, MTA apex: −3.30% ± 14.14% ($p < .05$) Root length: revasc: 9.51% ± 18.14%, MTA apex: 8.55% ± 8.97% ($p > .05$). Revasc wide range in root lengthening: −4% to 58% Based on aetiology: DE: mean root length 15.1% ± 22.7%, mean root width 22.53% ± 25.2% caries: mean root length 5.3% ± 3%, root width −0.42% (only 1 case) trauma: mean root length 0.49% ± 4.4%, mean root width 6.4% ± 8.8%

First author, country	Arslan H, Turkey	Brizuela C, Chile	Jha P, India	Lin J, China	Silujjai J, Thailand
Radiographic evidence of reduction of apical lesion size	Absence of the periapical lesion: CRCT: 60%, REP: 46.2% Reduction in the periapical lesion: CRCT: 25%, REP: 46.2% Uncertain: CRCT: 15%, REP: 7.7%	Significant difference (Mann–Whitney test $p = .0082$) between the groups only in the reduction in the anteroposterior dimension between 6 and 12 m, with a median reduction of 0.35 mm in CRCT and 0.94 mm in REP	At 18 m: mean PAI-score: SealBio: 1.1 ± 0.35 NSRCT: 1.2 ± 0.41 ($p = .62$)	All included: 100% lesion reduction	MTA apex: 80.77% revasc: 76.47%
Radiographic evidence of normal periodontal ligament space	Absence of the periapical lesion (= if the postoperative radiographic periodontal space was smaller than 0.5 mm): CRCT: 60% REP: 46.2%	Not specifically reported	Radiographic normalcy at 18 m: SealBio: 13/15 NSRCT: 12/15	Not specifically assessed	Not assessed
Tooth function[b]	Sufficient quality of coronal restoration: CRCT: 100% REP: 88.5%	At 12 m: no fracture and no restoration failure	Fracture: none No reports concerning coronal restorations	Fracture: none All coronal restorations survived	MTA apex: 5 root fractures
Need for further intervention	Not reported	None	None	Not reported	Revasc: 3 persistent infection, 1 reinfection, all signs of AP
Presence of sinus tract	CRCT: pre: 35%, post: 15%; REP: pre: 19.2%, post: 7.7%	None	Pre: not reported Post: none	None	Revasc: in 4 cases that needed further intervention
Tooth survival	Not reported	All included	All included	At 12 m: all assessed teeth survived (100%)	Functional retention: MTA apex: 82.76%, revasc: 88.24%
Adverse events[c]	REP: 38.5% discoloured ($p < .05$)	None	None	External root resorption: 2 in trauma subgroup REP: 30 discolouration, 26 calcification	See 'need for further intervention' Revasc: 4 cases calcified root canal
OHRQoL	Pre- and postoperative pain and percussion pain: measured via VAS. Pain on percussion: CRCT: pre: 32.10 ± 33.43, 7d post: 0 REP: pre: 36.15 ± 21.00, 7d post: 0	Not specifically assessed	Not specifically assessed	Not specifically assessed	Not assessed

First author, country	Arslan H, Turkey	Brizuela C, Chile	Jha P, India	Lin J, China	Silujjai J, Thailand
Response to sensibility testing	REP: 50% ($p < .05$)	At 12 m: Cold test: CRCT 6%, REP 56% Hot test: CRCT 0%, REP: 28% Electric test: CRCT: 17%, REP: 50% Doppler flowmetry: REP: an increase of perfusion unit from baseline, 6 and 12 m: 60.6% to 74.4% to 78.1%	Not assessed	Not reported	Not assessed
Other results (quantitative and qualitative)	Success: CRCT: 80% REP: 92.3% ($p > .05$)	Safety and efficacy: at 12 m 100% success for both groups	*Final outcome at 18 m: SealBio: 13 healed, 2 healing NSRCT: 12 healed, 3 healing ($p = .62$) *Mean time treatment procedures: SealBio: 16.02 min. NSRCT: 36.59 min. ($p < .05$)	All analysed cases at 12 m ($n = 103$): successful	*Success rates*: Based on groups: MTA apex 80.77% revasc 76.47% ($p > .05$) Based on aetiology: trauma: 85% DE: 72.22% caries: 80% ($p = .292$) *Functional retention*: MTA apex: 82.76% revasc: 88.24% ($p > .05$)
Funding	None	Grant from 'Corporación de Fomento de la Producción' (CORFO[d]), project number L214IDL2–30051, Santiago, Chile	None	Supported by Sun Yat-sen University Clinical Research 5010 Programme (no. 2012016)	Not mentioned

[a]Antibiotics, analgetics.

[b]Fracture, restoration longevity.

[c]Exacerbation, restoration integrity, allergy, discolouration.

[d]Chilean Economic Development Agency.