



Influence of sealer type on treatment outcome of teeth with apical periodontitis: a systematic review

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The purpose of this article was to evaluate the influence of sealer on the outcome of non-surgical endodontic treatment or retreatment of permanent teeth with apical periodontitis (PROSPERO registration: CRD42020205951). Methodology: A systematic review of original clinical studies was carried out following PRISMA guidelines to answer whether the type of sealer used in endodontic treatment or retreatment influences the repair of apical periodontitis determined by clinical and radiographic parameters. Electronic searches were performed in PubMed, Embase, Web of Science, Scopus, and the Cochrane Library database, until May 2023. Gray literature and a hand search of reference lists were also performed. The risk of bias was assessed using Cochrane RoB2 for randomized trials and the Newcastle–Ottawa Scale (NOS) for prospective and retrospective cohort and case-control studies. Results: Among 1046 studies, a total of 819 were selected by title and abstract, resulting in 23 for full-text review. In total, 11 studies met the inclusion criteria (1467 patients/teeth with apical periodontitis). The quality assessment using RoB2 included five randomized control trials, of which four had medium risk and one had a low risk of bias. According to the NOS scale, five studies were classified as low risk and one study was considered as medium risk of bias. The sealer type and obturation techniques varied, and the mean follow-up time was 3.7 years. Most studies used two-dimensional radiographic criteria to assess the treatment outcome. Eight studies did not find significant differences when comparing sealers. The healing rates ranged from 56.7% to 90%. Conclusions: The results of this review support that the current endodontic sealers do not seem to influence the treatment outcome of permanent teeth with apical periodontitis. Although the studies had medium and low risk of bias, the results should be interpreted with caution. More randomized studies of long-term outcomes comparing filling materials are needed to strengthen this claim and allow for a meta-analysis.

Introduction

The main objectives of root canal obturation are to prevent infection or reinfection of the root canal system and negate access of residual bacteria to the periradicular tissues [1]. Filling materials can be classified as core materials and sealers; the former occupy the major volume of the prepared canal, while the latter are used to fill not only the space between dentinal canal walls and the core material, but also other irregularities and complexities of the canal system. Sealers are generally classified as zinc oxide-eugenol-based, calcium hydroxide-containing, resinous, silicone-based, glass ionomer, and calcium silicate (or bioceramic) sealers. Because core materials are physically unable to reach and fill all areas and irregularities of the root canal system and have no ability to adhere to dentin, sealers play an essential role in promoting an adequate hydraulic and antibacterial seal [2-4].

Apical periodontitis is a highly prevalent disease in adult individuals [5] and the most conservative approach to treat this condition is nonsurgical endodontic treatment [6]. The success rate in teeth with apical periodontitis is significantly reduced when compared to teeth with no preoperative lesions [7]. Complete disinfection and subsequent sealing of the root canal system are essential for achieving endodontic success [6].

Earlier formaldehyde-containing sealers were developed with the purpose of fixating pulp tissue remnants and providing antimicrobial properties, but they have been demonstrated to be highly cytotoxic and compromise the periradicular tissue healing response when extruded [11], [12]. For the

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large majority of current root canal sealers cytotoxicity and antibacterial activities are observed following mixing and throughout the setting process [13, 14], but are mostly lost or significantly reduced when setting is complete [15, 16].

Studies have shown a lower healing rate in teeth with overfillings [9, 17], raising the possibility that this could be a result of the filling material cytotoxicity or a foreign-body reaction [18-22]. Therefore, the root canal sealer might have a biological influence on the treatment outcome. Several properties of these materials may potentially interfere with treatment outcomes, especially biocompatibility, sealing ability and antibacterial activity.

Outcome studies in humans comparing different filling materials are of great relevance to determine if they influence the result of root canal treatment. The aim of this systematic review is to evaluate the influence of root canal sealers on healing of apical periodontitis, as determined by radiographic and clinical parameters.

Material and methods

A systematic review of the best evidence available in the literature was performed following the most recent recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (<http://www.prisma-statement.org>) [23]. The review was registered on the international database of prospectively registered systematic reviews with a health-related outcome (PROSPERO) under number CRD42020205951.

Review question

The focused question was: 'In patients/teeth with apical periodontitis what is the influence of the type of sealer in root canal treatment or retreatment in terms of clinical and radiographic-related outcomes?'. The following PICOT strategy was used: (P) patients/permanent teeth with apical periodontitis subjected to root canal treatment or retreatment with (I) any root canal sealer in comparison with (C) any other root canal sealer and addressing (O) clinical and radiographic outcomes for (T) at least one-year post-op.

Eligibility criteria

- *Studies*: original clinical studies based on humans (randomized controlled clinical trials, nonrandomized clinical trials, retrospective and prospective comparative cohort and case-control studies);
- *Participants and intervention*: patients with apical periodontitis who have undergone root canal treatment or retreatment in permanent teeth, not subjected to periradicular surgery;
- *Comparison*: studies that addressed root canal treatment in permanent teeth and compared two or more sealers;
- *Outcome*: outcomes were a combination of clinical and radiographic outcome measures. The most critical outcomes were 'success rate' and radiographic evidence of apical healing. Other outcomes included clinical absence of signs and symptoms (such as pain, tenderness, swelling, need for medication)
- *Time*: studies with at least 1 year of follow-up.

The exclusion criteria were lack of information about the sample size, deciduous or immature permanent teeth, animal or *in vitro* studies, case reports, literature reviews, editorials, and annals/presentations in professional meetings.

Searching strategy

The searching process was performed independently by three examiners (SCB, ARP, and EST). The PubMed database (all years up to May 2023) was electronically searched by using the MESH and entry terms and the Boolean operators AND and OR. Further search was performed through Embase, Web of Science, Scopus, and the Cochrane Library database. Gray literature was also consulted, through IBICT (Brazilian Institute of Information in Science and Technology), Brazilian Digital Library of Theses and Dissertations (BDTD) and Google Scholar. A search was also performed on the reference lists of all selected articles (Box1).

Box. Search strategy.

Database	
PubMed/Medline	(((((((((Periapical Periodontitis[MeSH Terms]) OR (Periodontitis, Acute Nonsuppurative)) OR (Periodontitis, Apical)) OR (periapical lesion)) OR (apical lesion))) OR (cyst, radicular[MeSH Terms])) OR (periapical granuloma[MeSH Terms])) AND (((((((((((((((((((((((((((((Root Canal Filling Materials[MeSH Terms]) OR (Root Canal Filling Material)) OR (Root Canal Sealants)) OR (Sealants, Root Canal)) OR (Epoxy Resins[MeSH Terms])) OR (Epoxy Resin)) OR (epoxy resin-based root canal sealer[MeSH Terms])) OR (AH Plus)) OR (Adseal)) OR (Zinc Oxide-Eugenol Cement[MeSH Terms])) OR (Caryosan)) OR (Glass Ionomer Cements[MeSH Terms])) OR (Glass Ionomer Cement)) OR (Glass Polyalkenoate Cement)) OR (Glass Polyalkenoate Cements)) OR (Glass-Ionomer Cement)) OR (Polyalkenoate Cement)) OR (Polyalkenoate Cements)) OR (Calcium Hydroxide[MeSH Terms])) OR (mineral trioxide aggregate[MeSH Terms])) OR (MT aggregate)) OR (MTA cement)) OR (MTA-Fillapex)) OR (OrthoMTA)) OR (ProRoot (aggregate)) OR (RetroMTA)) OR (aggregate ProRoot)) OR (Bioceramic sealer)) OR (Dental Cements[MeSH Terms])) OR (Cement, Dental)) OR (Cements, Dental)) OR (Dental Adhesives)) OR (Dental Cement)) OR (Luting Agents)) OR (Root canal filling)) OR (Root Canal Obturation[MeSH Terms])) OR (Endodontic Obturation)) OR (sealer))) AND (((((((((((((((Treatment Outcome[MeSH Terms]) OR (Clinical Effectiveness)) OR (Clinical Efficacy)) OR (Patient-Relevant Outcome)) OR (Rehabilitation Outcome)) OR (Treatment Effectiveness)) OR (Treatment Efficacy)) OR (Outcome Assessment, Health Care[MeSH Terms])) OR (Assessment, Outcomes)) OR (Outcome Assessment (Health Care))) OR (Outcome Measures)) OR (Outcome Studies)) OR (Outcomes Assessment)) OR (Outcomes Research)) OR (Healing)) OR (Prognosis[MeSH Terms])))) AND (((((((Randomized Controlled Trial[MeSH Terms]) OR (Cohort Studies[MeSH Terms])) OR (Prospective Studies[MeSH Terms])) OR (Retrospective Studies[MeSH Terms])) OR (Case-Control Studies[MeSH Terms]))))
Scopus	TITLE-ABS-KEY "periapical periodontitis" OR "apical periodontitis" OR "periradicular lesion" OR "periapical lesion", "endodontic disease" AND TITLE-ABS-KEY "root canal filling materials" OR "endodontic sealer" OR "root canal obturation"
Embase	'periapical periodontitis'/exp OR 'apical periodontitis' OR 'periradicular lesion' OR 'periapical lesion' OR 'endodontic disease' AND 'root canal filling'/exp OR 'endodontic sealer' OR 'root canal obturation'
Cochrane Library	Apical periodontitis [MeSH-explode all trees] AND Endodontic Sealer [MeSH-explode all trees]
Web of Science	"periapical periodontitis" OR "apical periodontitis" OR "periradicular lesion" OR "periapical lesion", "endodontic disease" AND TITLE-ABS-KEY "root canal filling materials" OR "endodontic sealer" OR "root canal obturation"
Gray literature (Google Scholar, IBICT and BDTD)	Apical periodontitis AND Endodontic Sealer
Hand Research	Manual search of selected article references

The retrieved records were transferred to the EndNote Web® reference manager (EndNote web software, Clarivate Analytics, Philadelphia, PA, USA) to identify duplicates. A two-stage screening (titles and abstract first and then full-text) was carried out independently by two reviewers (PAS and SCB). When there was no agreement, a third examiner (ARP) was consulted and made the final decision. At the full-text stage, a data screening form was used to verify study eligibility, assess quality assessment and extract data on study characteristics and outcomes. The eligible studies were assessed for the outcome measures including 'success rate', radiographic/tomographic evidence of periradicular healing/reduction in lesion size, and clinical absence of signs and symptoms.

Quality assessment (risk of bias)

Two reviewers (PAS and SCB) analyzed the risk of bias separately. Disagreements were resolved by consulting the third reviewer (ARP). The quality assessment for randomized control trials was performed according to the *Revised Cochrane risk of bias tool for randomized trials – ROB2* [24–26]. This instrument is structured in five domains of bias: (1) randomization process, (2) deviations from the intended intervention, (3) missing outcome data, (4) outcome measurement, and (5) selection of the reported result. The judgments within each domain lead to an overall risk of bias judgment for the result being assessed. The judgment for each domain is "low risk of bias" (the study is judged to be at low risk of bias for all domains for this result), "some concerns" (the study is judged to raise some concerns in at least one domain for this result, but not to be at high risk of bias for any domain), or "high risk of bias" (the study is judged to be at high risk of bias in at least one domain for this result, or the study is judged to have some concerns for multiple domains in a way that substantially lowers confidence in the result). The overall risk of bias generally corresponds to the worst risk of bias in any of the domains. However, if a study is judged to have "some concerns" about risk of bias for multiple domains, it might be judged as at high risk of bias overall [26].

Furthermore, the NOS scale (*Newcastle-Ottawa Scale*) [28] was used for prospective and retrospective cohort and case-control studies, by categorizing them into three dimensions: selection, comparability, and exposure/outcome. The selection, comparability, and exposure dimensions contain four, two, and three items, respectively. A star system was used as a semi-quantitative assessment of the study quality. A study received a maximum of one star for each numbered item within the selection and exposure categories. A maximum of two stars were awarded for comparability. The number of stars ranged from zero to nine (high-quality, ≥ 7 stars; medium-quality, 4–6 stars; poor-quality, <4 stars) [29].

Data extraction

The extracted data was also performed by two independent reviewers (PAS and SCB) and included: authors and year of publication, study design, number of patients/teeth/roots/canals, primary treatment/retreatment, instrumentation technique/final apical diameter, irrigation technique/solution, intracanal dressing, type of sealer, obturation technique, final restoration, obturation quality assessment, follow-up, evaluation method, outcome.

Results

The results of the search strategy are shown in Figure 1. Database and hand search yielded 1,046 relevant references. After duplicate removal, 819 studies were screened by title and abstract, resulting in 23 potential articles for full-text review. Twelve were excluded as they did not completely meet the eligibility criteria (Box2): ten studies did not compare sealers [30–39], one study assessed teeth without apical periodontitis [40], and one study did not mention the number of patients, teeth, or root/root canal with apical periodontitis [41]. The remaining 11 articles (1,467 patients/teeth with apical periodontitis) were included in the qualitative synthesis: 1 non-randomized clinical trial [42], 5 randomized clinical trials [43–47], 3 retrospective studies [22, 48, 49], and 2 prospective cohort studies [50, 51]. The quality assessment using RoB2 is described in figure 2 and included five randomized control trials studies [43–47]. All the included randomized control trials received some concerns in the overall risk of bias.

The results of the NOS scale are shown in Box3. The evaluated studies which showed [22, 49–51] and 8 stars [48] were classified with a low risk of bias. One study [42] had 5 stars and was considered with medium risk of bias. The lack of stars for the above-mentioned studies was related to a lack of terms for the nonexposed cohort (related to study design), no description of the assessment outcome and follow-up rate <80%, without description of losses. The main extracted data are detailed in Box4. Supplementary data are presented in BoxS1. A variety of missing analyses was observed, such as tooth type, number of roots/canals, lesion size, different instrumentation and obturation techniques.

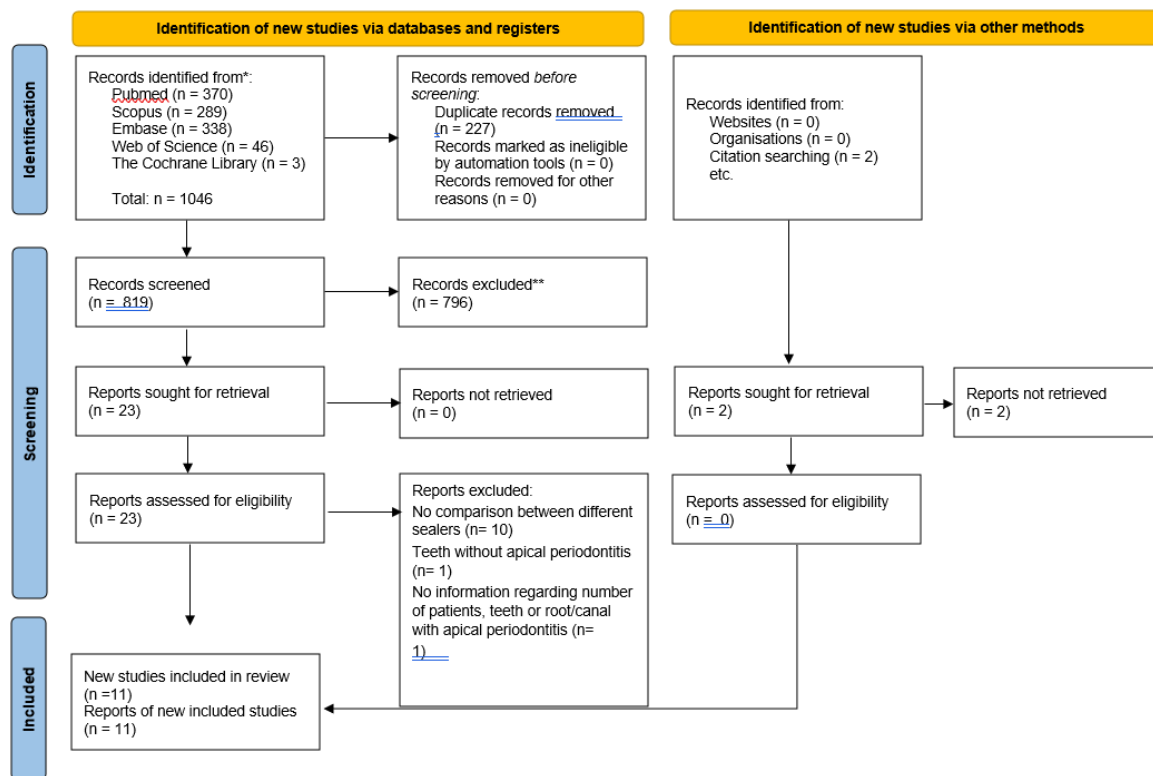


Figure 1. PRISMA flowchart with identification of the studies via databases and registers (PRISMA 2020 flow diagram).

Box 2. Excluded articles during full-text review.

Excluded articles by year of publication	Reason for exclusion	Sealer used
Friedman et al. 1995	Did not compare sealers.	(Ketac-Endo)
Waltimo et al. 2001	Did not mention the number of patients, teeth, or root/root canal with apical periodontitis.	(Procosol, CRCS, and Sealapex)
Molander et al. 2007	Did not compare sealers.	(Rosin chloroform)
Zmener & Pameijer 2012	Did not compare sealers.	(EndoRez)
Edionwe et al. 2014	Did not compare sealers.	(AH26)
Zhang et al. 2015	Did not compare sealers.	(AH Plus)
Kandemir Demirci & Caliskan 2016	Did not compare sealers.	(AH Plus)
Barborka et al. 2017	The study assessed teeth without apical periodontitis.	(Real Seal and AH Plus)
Eyuboglu et al. 2017	Did not compare sealers.	(AH Plus)
Chybowski et al. 2018	Did not compare sealers.	Endosequence Bioceramic Sealer
Olcaý et al. 2019	Did not compare sealers.	(AH Plus)
Llena et al. 2020	Two sealers were used; however, the authors did not compare them.	(AH Plus and Bioroot RCS)

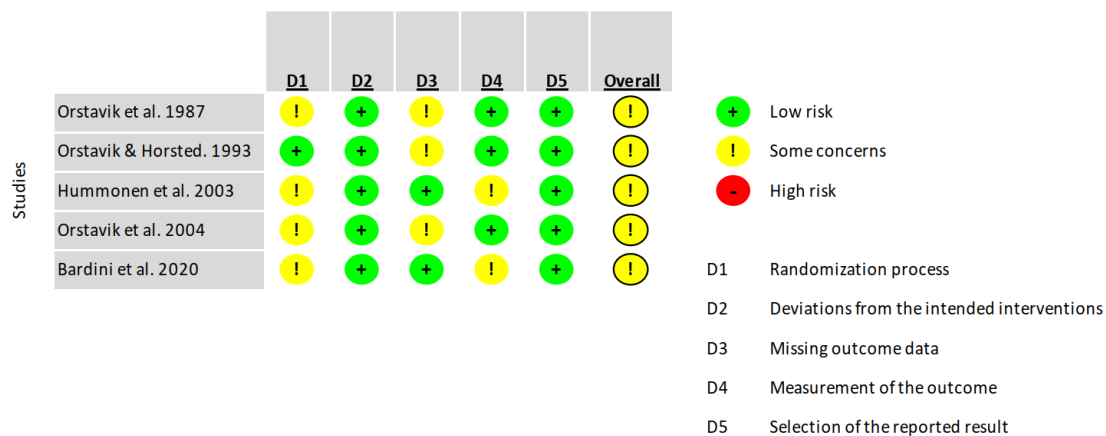


Figure 2. Risk of bias of the randomized clinical studies. (+) indicates a low risk of bias, (!) indicates some concerns, whilst (-) indicates a high risk of bias.

Box 3. Quality analysis of the cohort studies according to the Newcastle-Ottawa Scale (NOS).

		Cotton et al., 2008	Ricucci et al., 2011	Ricucci et al., 2016	He et al., 2017	Strange et al., 2019	Zavattini et al., 2020
Selection							
1. Representativeness of the exposed cohort	a. truly representative of the average in the community *	x	x	x	x	x	
	b. somewhat representative of the average in the community *						x
	c. selected group						
	d. no description of the derivation of the cohort						
2. Selection of the non-exposed cohort	a. drawn from the same community as the exposed cohort *						
	b. drawn from a different source						
	c. no description of the derivation of the unexposed cohort	x	x	x	x	x	x
3. Ascertainment of exposure	a. secure recorded (e.g., surgical records) *	x	x	x	x	x	x
	b. structured interview *						
	c. written self-report						
	d. no description						
4. Demonstration that the outcome of interest was not present at the start of the study	a. Yes*	x	x	x	x	x	x
	b. No						
Comparability							
1. Comparability of cohort on the basis of the design or analysis	a. study controls through imaging examinations (X-rays, CT scans) *	x	x	x	x	x	x
	b. study controls for additional factors (Side effects) *	x			x		

Box 3. Continuation

		Cotton et al., 2008	Ricucci et al., 2011	Ricucci et al., 2016	He et al., 2017	Strange et al., 2019	Zavattini et al., 2020
Outcome							
1. Assessment of outcome	a. independent blind assessment *	x	x	x		x	
	b. record linkage *						
	c. self-report						
	d. no description				x		x
2. Was follow-up long enough for outcomes to occur	a. Yes*	x	x	x	x	x	x
	b. No						
3. Adequacy of follow-up of cohorts	a. complete follow-up - all subjects accounted for *			x		x	
	b. subjects lost to follow up unlikely to introduce bias - small number lost - < 20% follow up, or description provided of those lost *	x	x		x		
	c. self-report						
	d. follow-up rate <80%, without description of losses						x
	e. no statement						
TOTAL * / Risk of bias		8/9	7/9	7/9	7/9	7/9	5/9

A star system was used for allowing a semi quantitative assessment of study quality. A study was awarded a maximum of one star for each numbered item within the selection and exposure categories. A maximum of two stars were awarded for comparability. The NOS ranges from zero to nine stars. The number of stars ranged from zero to nine (high-quality, ≥7 stars; medium-quality, 4–6 stars; poor-quality, < 4 stars).

The selected articles have not specified which tooth types had apical periodontitis. Only two studies [45, 47] specified the gender of the patients, totaling 243 patients (136 females and 107 males). However, no further detail of the number of teeth or roots/root canals with apical periodontitis was reported. Only one study [45] had 100% of the patients (n=199) with apical periodontitis. Nine studies reported the number of treated teeth with apical periodontitis [42, 44, 46–52], which ranged from 45 to 285, totaling 951 teeth. One study reported just the number of treated roots with radiographic periapical lesion (233 roots with periapical index [PAI] scores 3, 4 and 5) [43] and one [46] reported the number of roots with apical periodontitis, dividing them as single or multiple roots. Finally, regarding the number of root canals, one study reported that 15 single canals and 50 multiple canals had apical periodontitis [48], and other reported 359 root canals with apical periodontitis [50].

Root canal treatment or retreatment

Six studies performed primary root canal treatment [42, 43, 45, 46, 49, 52], while four studies performed both treatment and retreatment [44, 47, 48, 50]. One study [51] performed only retreatments. Root canal preparation was performed with several manual or rotary instrumentation and apical sizes varied from 25 to 40.

Root canal irrigation and intracanal medication

A variety of information regarding root canal irrigation and intracanal dressing between appointments was found among the studies, many of which missing a detailed description. Irrigant solutions included 0.5%, 1%, 2%, 5% and 5.25% sodium hypochlorite (NaOCl) and 5% chloramine-T; 17% EDTA and hydrogen peroxide were also mentioned. Syringe needle irrigation was the most used approach, while the use of passive ultrasonic irrigation and sonic activation of irrigant with the EndoActivator device was reported as supplementary irrigation methods in two studies [42–51].

Box 4. Data extracted from the selected studies.

Authors, year	Study Design	Number of patients (gender)/ teeth with AP	Number of roots with AP	Number of root canals with AP	Primary treatment (PT) or Retreatment (R)	Sealer used	Evaluation method	Follow-up
Orstavik et al., 1987	Randomized clinical trial	Not informed	233 roots with AP	Not informed	PT	AH26, Kloroperka N0, and Procosol	PAI Score	1 to 4 years
Orstavik & Horsted-Bindslev 1993	Randomized clinical trial	89 teeth with AP	Not informed	Not informed	PT and R	AH 26 and Kloroperka N0	PAI Score	1 to 4 years
Huumonen et al., 2003	Randomized clinical trial	199 patients (105 females and 94 males) / 36 incisors, 18 canines, 80 premolars, and 65 molars	Not informed	Not informed	PT	Roeko seal silicone-based sealer and Grossman type sealer	PAI Score	3 and 12 months
Orstavik et al., 2004	Randomized clinical trial	192 teeth with AP	133 teeth with one root; 32 teeth with 2 roots and 27 teeth with 3 roots		PT	AH 26 and Kloroperka N0 and Procosol	PAI Score	0.5–1 year, 2, 3, and 4 years
Cotton et al., 2008	Retrospective	65 teeth with AP (31 male and 34 female)	Not informed	Single canal (n= 15), multiple Canals (n = 50)	PT and R	Kerr Pulp canal sealer, Resilon and Epiphany sealer	PAI Score	2 to 25 months
Ricucci et al., 2011	Prospective cohort study	285 teeth with AP	Not informed	359 root canals with AP	PT and R	AH26, Bioseal, Pulp Canal Sealer, Tubliseal, Apexit, Mynol, and Endomethasone	Rigid criteria, based on both clinical and Strindberg's criteria	5 years
Ricucci et al., 2016	Retrospective	75 teeth with AP	Not informed	Not informed	PT	Pulp canal sealer, PCS (EWT), Tubli-Seal, Endomethasone, AH Plus and Apexit	Strindberg's criteria	1 year, 2 years and > 4 years

Box 4. Continuation.

Authors. year	Study Design	Number of patients (gender)/ teeth with AP	Number of roots with AP	Number of root canals with AP	Primary treatment (PT) or Retreatment (R)	Sealer used	Evaluation method	Follow-up
He et al., 2017	Prospective	45 teeth with AP	Not informed	Not informed	R	AH Plus sealer or Resilon and RealSeal	3 categories: 1. Healed: absence of any clinical signs or symptoms and normal periapical tissue with intact periodontal ligament space and lamina dura or a slightly widened periodontal ligament around extruded material 2. Healing: absence of any clinical signs or symptoms and periapical radiolucency still present but reduced in size 3. Nonhealing: presence of signs or symptoms and/or the emergence of new periapical radiolucency or unchanged or enlarged periapical radiolucency	6, 12 and 24 months
Strange et al., 2019	Retrospective	54 teeth with AP	Not informed	Not informed	PT	Resilon with Epiphany and AH Plus with gutta Points	PAI Score	The average follow-up periods for Resilon and gutta-percha were 12.4 years and 12.1 years, respectively
Zavattini et al., 2020	Nonrandomized clinical trial	178 teeth with AP	Not informed	Not informed	PT	AH Plus & Bioroot RCS	CBCT and radiographic analysis. Loose criteria	12 months
Bardini et al., 2021	Randomized clinical trial	44 patients (31 women and 21men) / Total: 52 teeth with AP	Not informed	Not informed	PT and R	Bio Root RCS and Pulp Canal Sealer	PAI Score	1, 3, 6 and 12 months

AP: Apical periodontitis; PAI: periapical index

Regarding interappointment intracanal medication, calcium hydroxide was the most used substance, while iodoform or metacresyl acetate applied on a cotton pellet were also reported. However, some studies failed to specify the type of medication used between appointments or if it was used at all [42-44, 47, 49].

Type of sealers and obturation techniques

The type of sealers used for root canal obturation varied from zinc oxide-eugenol-based [43, 46-48, 50, 52], epoxy resin-based [42-44, 46, 49-52], calcium hydroxide-containing [50, 52], bioceramic [42, 47], chloroform-gutta-percha [43, 44, 46], silicone-based [45], and methacrylate sealers [51], and dual-cure dental resin composite sealer with thermoplastic synthetic polymer-based solid material [48, 49]. Diverse obturation techniques were used, including lateral compaction [43-46, 50, 52], continuous wave of compaction [48, 51], single cone technique [42, 47] and warm vertical compaction [42, 47]. One study did not mention the obturation technique used [49]. Regarding funding sources, only two studies reported that they received support from industry [45, 42].

Not all authors informed the type of final restoration placed after root canal treatment [43, 44, 46, 49, 50], while others varied from direct composite as permanent build up [42, 47, 48, 51, 52], full cusp coverage [42], indirect restoration with full cusp coverage 52 or amalgam 48, and provisional materials such as IRM or Cavit [48, 51].

Clinical and Radiographic Follow-up

Clinical and radiographic follow-up periods ranged from 1 to 12.4 years [47, 49] with a mean overall follow-up time of 3.7 years. To evaluate the outcome of root canal treatment, most studies [43-49] used the 2-dimensional radiographic PAI score method [53], while others [50, 52] used the Strindberg's criteria [54]. Another study classified the treatment outcomes by defining 3 categories based on digital periapical radiographs: healed, healing and nonhealing [51]. Finally, only one recent study [42] used cone-beam computed tomography (CBCT) along with periapical radiographs for an outcome analysis defined by loose criteria (reduction in lesion size) [55].

Outcomes

Eight studies found no significant differences when comparing sealers [42, 44, 46-48, 51, 52] (Box5). The healing rates ranged from 56.7% [47] to 90% [51]. Ricucci *et al.* [52], compared six types of sealers, but evaluated only cases of unintentional overfillings. They found no statistically significant difference in the outcome between the sealers. Relatively new endodontic sealers (bioceramics) were compared in two recent clinical studies [42, 47]. The success rates for BioRoot RCS and Pulp Canal Sealer (PCS) were 76.9% and 56.7%, respectively; this difference however was not statistically significant ($p>0.05$) [47]. Another study found that BioRoot RCS in combination with single cone resulted in a success rate comparable to that of warm vertical condensation and AH Plus sealer ($p>0.05$).

The remainder of the studies found different responses to periapical healing after endodontic treatment when different sealers were used (Box5). A study found worsening of periapical healing after one year when Kloroperka was used, which was even more significant ($p<0.05$) after the second and third years of follow-up, in comparison with AH 26 and Procosol sealer [43]. However, it is important to point out that Kloroperka is not a sealer per se. Additionally, according to Ricucci *et al.* [50], AH26, Bioseal, Mynol, and Apexit sealers had higher success rates at 5 years follow-up than PCS, Endomethasone, and Tubliseal in teeth with apical periodontitis. The success rate was also influenced by the size of radiographic lesion, and if it was treatment or retreatment. A long-term outcome study (12 years follow-up) showed that subjects with Resilon/Epiphany treated teeth were more likely to have an apical periodontitis lesion than teeth filled with gutta-percha/AH Plus [49]. Moreover, the adjusted odds ratio showed that teeth obturated with Resilon/Epiphany were 5.3 times more likely to have a lesion at follow-up than those treated with gutta-percha/AH Plus.

Box 5. Outcome of root canal treatment when two or more sealers were compared.

Study	Sealers	Statistical difference	Follow-up	Healing/success rate	Outcome
Orstavik et al. 1987	AH 26 Kloroperka NO, and Procosol	p<0.05	4 years	Presented as a graphic plot	Differential response to treatment is evident between Kloroperka and the two other groups. The poorer periapical situation associated with roots treated with Kloroperka was already statistically significant after 1 year, but became more pronounced after 2 years and even more after 3 years. Also, in all comparisons, it was evident that AH 26 and/or ProcoSol performed better than Kloroperka.
Orstavik & Horsted-Bindslev 1993	AH 26 vs. Kloroperka	p>0.05	4 years	Presented as a graphic plot	Statistical analyses by ridit or chi-square failed to suggest any difference between Kloroperka and AH26 sealers.
Huumonen et al. 2003	Roeko Seal silicone-based vs. Grossman type sealer	p>0.05	12 months	Overall (76%)	The overall 'success' rate at 12 months was 76%. Average PAI scores decreased from 3.43 at start to 2.21 at 12 months for GS and from 3.40 to 2.26 for RS. In both sealer groups, there was a statistically significant decrease of PAI scores after root-canal filling at 3- and 12-months examinations compared to the time of filling. There was no statistically significant difference in healing after treatment with RS compared to GS, expressed as either 'success rate' or 'improvement'
Orstavik et al. 2004	AH 26 and Kloropeka NO and Procosol	p>0.05	4 years	Overall (79%)	In the CAP group, out of 192 treated teeth, 21% of treatments were classified as failure. In a separate univariate analysis statistics, the choice of sealer had no significant effect on the treatment outcome.
Cotton et al. 2008	Kerr Pulp canal sealer (PCS) vs. Resilon and Epiphany sealer	p>0.05	25 months	66%	No statistically significant association was detected between the type of obturation material and the outcomes of healed or non-healed. From 65 teeth with preoperative radiolucency and recall times from 2 - 25 months: 66.2% healed and 33.8% did not healed. At 12-25 months observations > 18 months (long) 33 healed (75 %) 11 Non-healed (25%) 12-18 months (intermediate) 5 healed (83.3%) 1 non-healed (16.7%) < 12 months (short) 5 healed (33.3%) 10 non-healed (66.7%)
Ricucci et al. 2011	AH26, Bioseal, Apexit, Mynol, Pulp Canal Sealer, Tubliseal, and Endomethasone	p<0.001 (comparison between two large groups: the 4 former sealers vs. the 3 latter ones)	5 years	82.7%	If the pulp necrosis was complicated by apical periodontitis, the success rate fell to 82.7% for the tooth and 84.1% for the root canals. These differences are statistically significant for the root canals (P = .037). Teeth with periapical lesion ≤ 5 mm had a success rate of 86.6%, and the cases where the lesion was ≥ 5 mm the rate of success was 79.4%. Teeth undergoing retreatment had a success rate of 90.5%. The failures in this group, however, were entirely clustered in the cases with apical periodontitis, which were successful in 83.3%. When studying the outcome, it is obvious that AH26, Bioseal, Mynol, and Apexit are clustered at a higher rate of success than Pulp Canal Sealer, Endomethasone, and Tubliseal.
Ricucci et al., 2016	Pulp canal sealer, PCS (EWT), Tubli-Seal, Endomethasone, AH Plus and Apexit	p>0.05	4 years	79%	At the 1-year recall, from 43 teeth with AP: 20 (46.5%) healed and 14 (33%) teeth were healing (lesion reduced in size but still present). At the 2-year recall, from 52 teeth; 31 (60%) and 12 (23%) were healed and healing, respectively. At >4-year follow-up 79% of the cases with PA healed. There was no statistically significant difference in the outcome between the tested sealers at all examination periods
He et al., 2017	AH Plus sealer and Resilon vs RealSeal sealer	p>0.05	24 months	Real Seal (90.00%), AH Plus (90.09%)	37 (71.2%) patients showed complete healing at the last follow-up visit. Ten (19.2%) patients remained asymptomatic throughout the follow-up period and showed a reduction in their periapical lesion size; however, lesions that were not completely resolved at the last follow-up visit were considered as "healing." Five (9.6%) patients had a persistent (3) or new (2) periapical lesion. Three were asymptomatic, and 2 reported "occasional discomfort" or "sensation" on the treated tooth. The overall success rate, combining "healed" and "healing" cases, was 90.4%. All teeth remained functional. Twenty-two cases were obturated with GP, and 30 were obturated with RS. Three failures were noted in the RS group and 2 in the GP group, resulting in a success rate of 90.0% and 90.9%, respectively. Nineteen of 30 (63.3%) in the RS group and 18 of 22 (81.8%) in the GP group showed complete healing.

Study	Sealers	Statistical difference	Follow-up	Healing/success rate	Outcome
Strange <i>et al.</i> 2019	Epiphany vs. AH Plus with gutta Points	$p < 0.01$	12 years	Not mentioned	Resilon-treated teeth were more likely to have a periapical lesion at follow-up than gutta-percha. This difference was statistically significant, and the adjusted odds ratio indicated that Resilon-treated teeth were 5.3 times more likely to have a lesion at follow-up when compared with gutta-percha even after controlling for the presence of a preoperative lesion and the length to follow-up. The findings suggested that a tooth with a preoperative lesion, regardless of the material used, was more likely to have a follow-up lesion.
Zavattini <i>et al.</i> 2020	BioRoot RCS vs. AH Plus sealer	$p > 0.05$	12 months	AH Plus (80%) and BioRoot (84%)	The success rate using loose criteria for the CBCT images was 80% in the AH plus/warm vertical. The success rate using loose criteria for the CBCT images was 80% in the AH plus/warm vertical condensation group (41 success/10 failure) and 84% in the BioRoot RCS /single cone group (45 success condensation group (41 success/10 failure) and 8 in the BioRootTM RCS /single cone group (45 success, 8 failure). The success rate using loose criteria for the periapical radiographs was 89% in the AH plus/warm vertical condensation group (45 success/6 failure) and 90% in BioRoot RCS/single cone group vertical condensation group (45 success/6 failure) and 90% in the BioRoot RCS/single cone group (48 success/5 failure).
Bardini <i>et al.</i> 2021	BioRoot RCS vs. Pulp canal sealer	$p > 0.05$	12 months	BioRoot (76.92%) PCS (56.67%)	The success rate at 12 months was higher in the BIO group than in the PCS group (76.92% versus 56.67%). Similarly, the survival rates in the BIOAP and PCSAP groups were comparable at 12 months, and the healing rate was higher in the BIOAP group than in the PCSAP group (67.86% versus 50%), but the difference was not statistically significant ($p > 0.05$).

Discussion

This systematic review focused on the question of whether the type of root canal sealer can influence the outcome of the nonsurgical root canal treatment or retreatment of teeth with apical periodontitis. A recent systematic review [7] investigated if obturation techniques and materials used for root canal filling influenced the treatment of apical periodontitis. The authors found very heterogeneous data and a high risk of bias of the included studies. As for sealers, the previous review was limited to studies comparing 2 sealers (AH Plus and AH26) with any other; as such, only two studies were included for the analysis of sealers. The present review in turn focused on any comparisons involving sealers, which resulted in the selection of 11 studies, most of which with a medium risk of bias. Findings from both studies indicate that the treatment outcome is not affected by sealers.

One noBox exception is the Resilon/Epiphany (Resilon Research LLC, Madison, CT). Although a preliminary short-term study (1 to 2-year follow-up) reported comparable results between Resilon/Epiphany and gutta-percha/Kerr Pulp Canal Sealer (Kerr corporation, Orange, CA, USA) (Cotton *et al.*, 2008), long-term data (> 5 years) revealed a significantly worse outcome in the former [40, 49]. Barborka *et al.* [40] observed that 56% of the teeth filled with Resilon/Real Seal SE were successful as compared to 88% of the gutta-percha-AH Plus-filled teeth. In another study [49], teeth filled with Resilon/Epiphany exhibited 5.3 times higher prevalence of apical periodontitis when compared with gutta-percha/AH Plus. The reasons for the worst results presented by Resilon/Epiphany may be related to enzymatic degradation of the material and creation of a gap between the sealer and the core [56], failure to resist shrinkage stress [57], and high cytotoxicity [58].

Apart from the old data on Kloroperka (a filling material based on gutta-percha softened in chloroform) and the most recent ones on Resilon/Epiphany, there is only one cohort study showing significant different outcomes according to the sealer type. In a prospective cohort study, Ricucci *et al.* [50] found that collectively the sealers AH26, BioSeal, Mynol, and Apexit, all with more than 92% success rate, had better outcomes at 5-year follow-up when compared to PCS, Endomethasone, and Tubliseal, with less than 88% success. However, the sealers were included in two groups for statistical analysis. We used the data available in the article for a pairwise comparison between sealers using the chi-square test with Yates correction and the only differences observed were for PCS compared with Apexit or Bioseal ($p < 0.05$). Moreover, no distinction was made in the article as for the periradicular

status before treatments. Therefore, it is not possible to ascertain the influence of these sealers in teeth with apical periodontitis only, which is the purpose of this systematic review.

All the other studies included showed that the root canal sealer does not exert a significant influence on the outcome of the root canal treatment of teeth with apical periodontitis. This is in agreement with a previous systematic review of diverse clinical factors with potential to influence the treatment outcome [59].

Some relatively new materials, including calcium silicate-based or bioceramic sealers, have not been used in clinical practice for sufficient time to be assessed in long-term outcome studies. Consequently, there is limited information about their influence on treatment outcome. Calcium silicate-based sealers have shown promising physicochemical and biologic properties in comparison with conventional sealers [60–62]. However, the few outcome studies published so far show no improved results in comparison with conventional materials [42, 47].

A study evaluating the fate and influence on the treatment outcome of different sealers that were accidentally extruded to the periapical tissues demonstrated that, while there were differences in the removal rate of the different materials over time, none of them was shown to influence the outcome of teeth with or without apical periodontitis [52]. Teeth with preoperative apical periodontitis showed a worse outcome, but with no difference between the different materials. The main causes of a compromised outcome in teeth with extruded material overfilling have been suggested to be related to an inadequate apical seal or previous overinstrumentation, and not the effects of the material itself [63]. In spite of being exclusively focused on the outcome of overfillings, that study was included in the systematic review because it represented the extreme of contact area between the filling material and the periradicular tissues.

Unlike several cytotoxic filling materials used in the past, the large majority of current materials may exhibit some cytotoxicity before setting [64–66]. As demonstrated in many short-term animal studies [67–69], these materials can be associated with an inflammatory response of varying intensity in the periodontal ligament tissue area in contact with the material. In overfillings, the material volume and the contact area are larger, and consequently the inflammatory response is more severe [70]. However, because most filling materials lose their toxicity with the passage of time [71, 72], the tissue aggression is not sufficient to cause or sustain an apical periodontitis lesion. Therefore, in the absence of concurrent residual infection, most currently available filling materials per se may not influence the outcome of the endodontic treatment, as demonstrated by most studies reviewed herein. Despite a few reports in the literature [19, 73], the present findings also suggest that most current filling materials do not cause a foreign-body reaction, and as such are not the cause of posttreatment apical periodontitis.

Many properties of root canal filling materials might potentially interfere with the treatment outcome, especially cytotoxicity, sealing ability, and antibacterial activity. If the material is too toxic to human cells, it can cause tissue damage and lead to or maintain inflammation. Materials that fail to promote an adequate seal permit seepage of inflammatory exudate or tissue fluid into the canal, providing residual bacteria with nutrients to grow and cause or maintain apical periodontitis [74]. Materials with antibacterial properties may contribute to additional disinfection by killing residual bacteria [16, 75]. These properties are influenced by many others including adhesion to dentin, solubility, dimensional stability, and flow ability. The literature is plenty with *in vitro*, *ex vivo* and animal studies evaluating the properties of endodontic filling materials [62, 76–79]. Despite the differences usually reported in most of these studies for different sealers, this systematic review suggests that such differences may not suffice to represent benefits in terms of improved outcome for any of the sealers currently available. The treatment steps involved with infection control before obturation are expected to have more impact on the treatment outcome [9, 10].

The present study has not evaluated if the type of material can influence the healing time. Some studies have reported longer healing times for some overfilled teeth [52, 82], but whether the reasons for that are the filling material type, concomitant low-grade infection and/or host-related factors remain to be elucidated.

This systematic review has certainly limitations. The main shortcoming is that there is a remarkable scarcity of prospective studies about the long-term management and outcome of patients with apical periodontitis. This is especially true for randomized controlled clinical trials. The heterogeneity of the selected articles was evident right from the beginning. Also, a variety of missing analyses was observed, such as tooth type, number of roots/canals, lesion size, different instrumentation and obturation techniques. In context, it was not possible to conduct a meta-analysis

because the data were widely dispersed, and the studies were very heterogeneous, with several methodological differences. Moreover, subgroup analysis (gender; age; size of the lesion; type of tooth; number of root canals) could not be performed in this review due to the lack of data from the selected studies. In addition, it is known that there are many variables that can influence the treatment outcome, such as the instrumentation technique and the irrigants used, tooth type, and host-related factors (age, systemic condition, etc.).

Based on this systematic review of clinical outcome studies, the current endodontic sealers do not seem to influence the treatment outcome of teeth with apical periodontitis. Although the studies were of medium and low risk of bias, the results should be interpreted with caution. Further randomized long-term outcome studies comparing filling materials are required to strengthen this assertion and permit a meta-analysis to be conducted. Despite differences between studies for different sealers, this systematic review suggests that such differences may not be sufficient to represent benefits in terms of better outcome for any of the currently available sealers.

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Resumo

O objetivo deste artigo foi avaliar a influência do cimento no resultado do tratamento ou retratamento endodôntico não cirúrgico de dentes permanentes com periodontite apical (registro PROSPERO: CRD42020205951). Metodologia: Uma revisão sistemática de estudos clínicos originais foi realizada seguindo as diretrizes PRISMA para responder se o tipo de cimento usado no tratamento ou retratamento endodôntico influencia a reparação da periodontite apical determinada por parâmetros clínicos e radiográficos. Pesquisas eletrônicas foram realizadas no PubMed, Embase, Web of Science, Scopus e no banco de dados Cochrane Library, até maio de 2023. A literatura cinza e uma pesquisa manual das listas de referências também foram realizadas. O risco de viés foi avaliado usando Cochrane RoB2 para os estudos randomizados e Newcastle-Ottawa Scale (NOS) para coorte prospectiva e retrospectiva e estudos de caso-controle. Resultados: Entre 1.046 estudos, um total de 819 foram selecionados por título e resumo, resultando em 23 para revisão de texto completo. No total, 11 estudos preencheram os critérios de inclusão (1.467 pacientes/dentes com periodontite apical). A avaliação de qualidade usando RoB2 incluiu cinco estudos randomizados de controle, dos quais quatro tinham risco médio e um tinha baixo risco de viés. De acordo com a escala NOS, cinco estudos foram classificados com baixo risco e um estudo foi considerado com médio risco de viés. O tipo de cimento e as técnicas de obturação variaram, e o tempo médio de acompanhamento foi de 3,7 anos. A maioria dos estudos utilizou critérios radiográficos bidimensionais para avaliar o resultado do tratamento. Oito estudos não encontraram diferenças significativas ao comparar os cimentos. As taxas de reparação variaram de 56,7% a 90%.

Conclusões: Os resultados desta revisão suportam que os cimentos endodônticos atuais não parecem influenciar o resultado do tratamento de dentes permanentes com periodontite apical. Embora os estudos tiveram médio e baixo risco de viés, os resultados devem ser interpretados com cautela. Mais estudos randomizados de resultados de longo prazo comparando materiais de obturação são necessários para fortalecer essa afirmação e permitir uma meta-análise.

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Appendix

BoxS1 – Supplementary data of the selected studies.

Authors. year	Instrumentation technique / final apical diameter	Irrigation technique / irrigation solution used	Intracanal dressing	Obturation technique	Final Restoration/ Quality assessment	Drop out (total)
Orstavik et al., 1987	Instrumentation was performed according to a standardized method, as described by Kerekes & Tronstad (1979).	Not specified / Technical variables, e.g., irrigants, dressings, complications including over-instrumentation, and sizes of instruments were recorded.	Not specified / Technical variables, e.g., irrigants, dressings, complications including over-instrumentation, and sizes of instruments were recorded.	Lateral condensation	Not informed	A substantial number of subjects (32.9%) failed to return for the 1-year recall examination (546 out of 810 roots). This percentage increased slowly up to 3 years (493 at 2 years and 451 at 3 years), followed by another major loss of patients at the 4-year recall 298 roots out of 810.
Orstavik & Horsted-Bindslev 1993	Instrumentation and filling were performed according to a standardized method, as described by Kerekes & Tronstad (1979).	Not specified / Technical variables, e.g., irrigants, dressings, complications including over-instrumentation, and sizes of instruments, were recorded.	Not specified / Technical variables, e.g., irrigants, dressings, complications including over-instrumentation, and sizes of instruments were recorded.	Lateral condensation	Not informed	Baseline was 282 teeth. At 1 year 216 teeth were available for follow-up examination, At 2 years 178, at 3 years 25 teeth and at 4 years 133 teeth were available for examination.
Huomonen et al., 2003	Technique not mentioned. Minimum size of ISO 35 was used for apical instrumentation.	Not informed	Calcium hydroxide	Lateral condensation	Not informed	At 12 weeks, 25 patients dropped out (n=172) At 12 months, 43 patients dropped out (84 out of 105 teeth for the RS group and 72 out of 94 teeth for the GS group). No differences were detected regarding group dropout.
Orstavik et al., 2004	All root canals were hand-instrumented with stainless steel reamers and files.	5% chloramine-T or NaOCl 0.5%.	Calcium hydroxide	Filling was performed according to a standardized method, as described by Kerekes & Tronstad (1979).	Not informed	135 roots representing 27 % of 810 roots.

BoxS1. Continuation

Authors. year	Instrumentation technique / final apical diameter	Irrigation technique / irrigation solution used	Intracanal dressing	Obturation technique	Final Restoration/ Quality assessment	Drop out (total)
Cotton et al., 2008	K3 0.04 or 0.06 taper / not reported	5,25% NaOCl warmed, final flush hydrogen peroxide and 17% EDTA.	Calcium hydroxide	Both obturation materials were incrementally down packed by using a System B (Sybron Endo) and condensers. After the down pack, the canals were backfilled by using an Obtura II gun (Obtura Spartan, Fenton, MO) with the same obturation material as the master cone.	Composite, Amalgam or a sterile cotton pellet followed by Cavit or IRM.	83 teeth with recall times ranging from 12–25 months.
Ricucci et al., 2011	Preflaring of the coronal two-thirds of the root canal with Gates-Glidden burs and hand instruments (Hedström files), the apical third was instrumented by hand instruments (Hedström and K-type files) using the “stepback” technique. Final diameter not described.	Syringe Needle / NaOCl 1%.	An intracanal antimicrobial dressing was placed in teeth undergoing multi-visit treatment. Slurry of calcium hydroxide, applied with a Lentulo spiral, was used in most cases. In some cases, instead of the calcium hydroxide, a small amount of metacresylacetate was applied on a cotton pellet and deposited in the pulp chamber. In a few cases, iodoform was applied	Lateral condensation	The authors describe than an appropriate restoration was placed, although details are not specified. The quality of restoration at the time of final evaluation was assessed clinically and on the periapical radiographs.	Of the 780 patients, 470 (60.3%) were available for the 5-year evaluation.
Ricucci et al., 2016	Gates glidden and hand instrumentation with Hedstrom and K-files/ Not informed	Syringe Needle / NaOCl 1%.	Calcium hydroxide	Lateral condensation	Direct restoration in cases with moderate tooth structure loss or indirect restoration when cuspal coverage was indicated.	From 105 patients: 1 year: 42 patients. 2 year: 32 patients and >4 years: 0 patients

BoxS1. Continuation

Authors. year	Instrumentation technique / final apical diameter	Irrigation technique / irrigation solution used	Intracanal dressing	Obturation technique	Final Restoration/ Quality assessment	Drop out (total)
He et al., 2017	Hand files and nickel-titanium rotary files in a crown-down approach / Mesial canal in mandibular molars and buccal canals in Maxillary molars, had a final apical size of 35 to 40 diameter and 04 to 06 taper. Distal and palatal canals had final apical sizes of #40 and 60 with taper of 04 and 06.	NaOCl, PUI. At the obturation visit, calcium hydroxide was removed with copious irrigation with 5.25% NaOCl combined with nickel-titanium rotary instrumentation. PUI was again used with NaOCl to ensure thorough removal of the medicament. The smear layer was removed with 5mL 17% EDTA.	Calcium hydroxide	Warm vertical compaction technique using System B and Obtura.	IRM temporary restoration. Permanent buildup was placed if it was requested by the referring dentist. All teeth received full-coverage crowns, which were determined to be adequate based on clinical and radiographic evaluation.	Fifty-four of the 63 patients returned for follow-ups. Two teeth were extracted before the 12-month follow-up. One was extracted because of a perforation created during post placement, and the other was extracted because of a vertical root fracture. Because these 2 early failures were excluded from the study, only 52 patients were available for the final analysis.
Strange et al., 2019	Not informed	Not informed	Not informed	Not informed	Not informed	-
Zavattini et al., 2020	Manual pre-enlargement (#20 flexofile) and Protaper Next instruments to a least a X2 file (25.06).	Syringe Needle / NaOCl 2% and 17% EDTA The irrigants were ultrasonically energized with a size 25 Endo-Activator for 1 min.	Not informed	Vertical condensation of gutta-percha and AH Plus and single cone technique for Bioroot.	Direct composite and full cuspal-coverage in some cases.	At baseline 25 teeth out of 150 were excluded for further follow-up. At 12 months, 21 patients (12 Ah plus and 9 Bioroot groups) up leaving a total of 104 for final assessment.
Bardini et al., 2021	Rotary instrumentation (protaper next) X1, X2 or X3 (when needed) for primary treatment and Gates glidden/hand instrumentation for retreatments (no final apical diameter cited for retreatment).	Not informed - NaOCl 5%.	Not informed	Single cone technique (Bio Root), and Warm Vertical Compaction with Pulp canal sealer.	Direct composite.	13 out of 55 patients