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Efficacy of Bioceramic Cements *Versus* Conventional Cements in the Prognosis of Endodontic Treatments in Patients with Apical Periodontitis: A Systematic Review with Meta-Analysis

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Abstract

Introduction: Successful management of apical periodontitis relies on effective root canal obturation to eliminate microbial activity and promote periapical healing. Bioceramic sealers have emerged as alternatives to conventional sealers due to their favorable biocompatibility and potential regenerative properties. However, their comparative clinical efficacy remains uncertain. **Materials and Methods:** A systematic review and meta-analysis were conducted following PRISMA 2020 guidelines. Four electronic databases (PubMed, Scopus, Web of Science, and Embase) were searched for randomized controlled trials (RCTs) comparing bioceramic and conventional sealers. Three reviewers independently performed study selection, data extraction, and risk of bias assessment using the RoB 2.0 tool. The primary outcomes were apical healing and postoperative pain; secondary outcomes included adverse events and procedural complications. Meta-analysis was performed using a random-effects model. **Results:** From 491 identified records, 12 RCTs met the inclusion criteria. Meta-analysis of four studies found no statistically significant difference in healing rates between bioceramic and conventional sealers (RR=1.05, 95% CI: 0.89-1.23, P=0.61; I^2=0%). No major adverse events were reported. Although bioceramic sealers have theoretical advantages, the current evidence does not support their clinical superiority over conventional sealers, as the meta-analysis showed non-significant results and some methodological limitations were identified. **Conclusion:** Bioceramic sealers appear to be clinically comparable to conventional sealers regarding periapical healing and postoperative outcomes. However, due to the limited and heterogeneous data, further high-quality RCTs with standardized outcome measures are needed to determine their relative effectiveness.

Keywords: Apical Periodontitis; Bioceramic Sealers; Conventional Sealers; Postoperative Pain; Systematic Review

Introduction

Apical periodontitis is a chronic inflammatory condition affecting the periapical tissues due to bacterial infections in the root canal system. It is characterized by tissue inflammation and destruction, often leading to bone resorption and potential tooth loss if untreated [1-4]. Persistent bacterial infections, inadequate mechanical debridement, and poor sealing of the root canal system primarily cause endodontic treatment failures. These issues highlight the need for effective techniques and materials to ensure proper sealing and promote healing [5-8].

The success of root canal treatment is significantly influenced by the quality of the apical seal, which is crucial for preventing bacterial infiltration and ensuring long-term treatment success [9-12]. Endodontic sealers are essential to endodontic treatment to ensure a hermetic seal of the root canal system, minimize spaces that could harbour microorganisms, and prevent reinfection [13, 14]. They work alongside core materials like gutta-percha to fill voids and enhance the seal between the root canal walls and the core material [15]. Bioceramic sealers have gained popularity in endodontics due to their unique properties, including biocompatibility, tissue

regeneration support, and antimicrobial effects. These attributes make them a promising choice for root canal treatments [16-19].

Bioceramic sealers and traditional resin-based sealers are both utilized in endodontic treatments, each with its own set of advantages [20, 21]. Current research indicates that both types of sealers perform similarly in terms of clinical outcomes, such as treatment success rates and postoperative pain [22-24]. The evidence regarding the superiority of bioceramic sealers over traditional resin-based sealers in terms of apical healing, postoperative pain, and long-term efficacy is currently limited and sometimes contradictory [25-27].

In clinical practice, the choice of endodontic sealer does not significantly impact the treatment outcomes of apical periodontitis. This conclusion is supported by multiple studies that have evaluated various types of sealers and their effects on healing and treatment success [28-30].

The current evidence does not demonstrate a significant improvement in clinical outcomes when using bioceramic sealers compared to conventional sealers in endodontic treatments [18, 20]. The need for a systematic review arises from the lack of clarity and consistency in existing research, which can impede effective decision-making and policy formulation. Systematic reviews provide a structured, transparent, and reproducible method for synthesizing research findings, thereby enhancing the reliability and applicability of evidence.

No prior systematic review has comprehensively synthesized RCT evidence focusing on both periapical healing and postoperative pain, two clinically relevant endpoints in endodontic prognosis.

The main objective of this study is the comparison between bioceramic cements versus conventional cements in the prognosis of endodontic treatments in patients with apical periodontitis, focuses on aspects such as apical healing, postoperative pain, long-term efficacy, and potential adverse events; to guide professionals in selecting the most suitable sealer for endodontic treatment of apical periodontitis, this synthesis reviews evidence on various sealers and their effectiveness in clinical outcomes.

Materials and Methods

Study Design

This study followed a systematic review design based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA 2020) guidelines. The PRISMA 2020 Checklist and Flow Diagram (Fig. 1) were used to ensure transparency and completeness in reporting the review process.

The study was registered with Prospero under the code: PROSPERO 2025 CRD420251061963. Searches: The PICO framework of our study was as follows: P: Patients with apical periodontitis undergoing root canal treatment I: Bioceramic sealers. C: Conventional sealers (*e.g.*, epoxy-resin, zinc oxide-eugenol) O: Periapical healing (primary); postoperative pain (secondary)

Literature searches were conducted using databases including PubMed, Scopus, Web of Science, and Embase. The search covered all records available up to August 25, 2024, utilizing key terms and thesauri such as MeSH (for PubMed) and Emtree (for Scopus, Embase, and Web of Science). A tailored search strategy was applied to each database.

The main search phrases were: (“apical periodontitis") AND (“periapical lesions") AND (“Silicates") AND (“Calcium Hydroxide”) AND (“Epoxy Resins”). There were no restrictions on language or publication dates. (Table 1)

Additionally, all reference lists of relevant studies and included review articles were manually screened to identify other potentially eligible trials.

Detailed electronic search strategy conducted across four databases (PubMed, Scopus, Web of Science, and Embase) up to July 25, 2024. The table presents the specific Boolean search strings applied for each database, including combinations of keywords and MeSH terms related to periapical periodontitis and root canal sealers, along with the total number of records retrieved.

Eligibility Criteria

Inclusion Criteria: This review included all randomized controlled trials (RCTs) that met the following criteria: (1) patients diagnosed with apical periodontitis undergoing endodontic treatment, and (2) studies comparing bioceramic sealers with conventional sealers. Eligible studies were required to report at least one primary outcome (periapical healing or postoperative pain) or secondary outcome (adverse effects or tooth survival).

Exclusion Criteria: The following types of publications were excluded: conference abstracts, systematic reviews, narrative reviews, case reports and case series, and letters to the editor.

Outcomes: Primary outcomes included periapical healing and the types of sealers used. Secondary outcomes were postoperative pain and the periapical index.

Data Extraction

After conducting electronic searches, results were compiled into a single reference library, and duplicates were removed. An initial screening of titles and abstracts was performed using the Rayyan platform, applying predefined inclusion and exclusion criteria.

The studies that were included after this phase were searched and analyzed in full text, and then a new screening process was

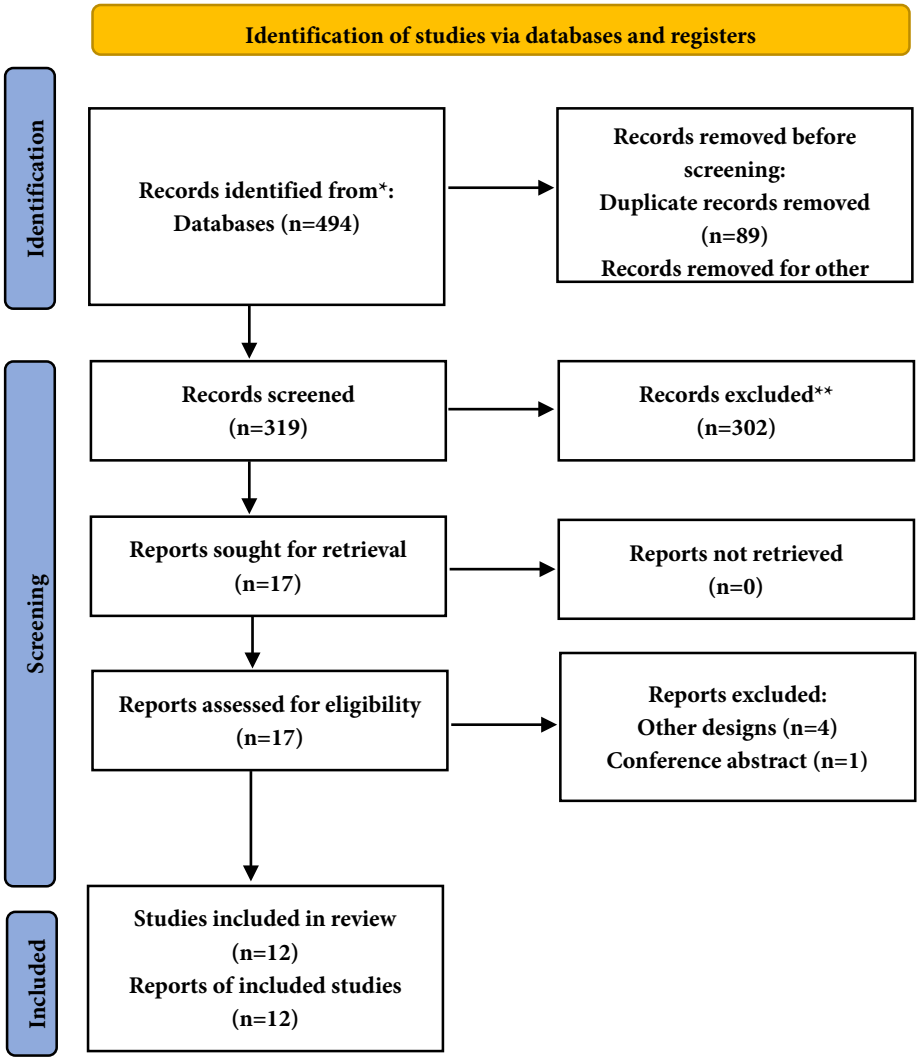

Figure 1. PRISMA flowchart for reviewing systematic review studies

carried out, justifying the inclusion and exclusion criteria. After this process, the resulting eligible studies were included in the systematic review, and data extraction began. In case of disagreement, a third review author was consulted.

For data extraction, a pre-prepared Excel spreadsheet format was used, and data were extracted from each study individually and blinded. Extracted variables included: author, year of publication, country, study design, number of participants in each group, selection criteria, description of the intervention and control arms (Table 2), and primary and secondary outcomes (Table 3).

Meta-analysis Procedures

Studies were included in the meta-analysis if they reported extractable and comparable outcome data related to periapical healing, including sample size, number of events per group, and follow-up duration. Only randomized controlled trials with clear dichotomous outcome measures for healing success and standard error estimates were eligible.

As this study was a systematic review of published data, ethical approval was not required. All included trials stated informed consent and local ethics approval.

Results

Data Synthesis

Selection of Studies: Figure 1 shows the PRISMA flow diagram of the identification, screening, exclusion, and inclusion of studies in this systematic review.

A total of 491 records were obtained from the databases; 175 duplicate records were removed. 307 reports were excluded using automatic filters or manually after selecting titles and abstracts, and reports were assessed for eligibility. Finally, 12 randomized controlled trials were included [12, 21, 25, 31-39].

Table 1. Search strategy used for database screening

Database	Search Strategy Search date: July 25, 2024		Results
PUBMED	#1	(#1=("Periapical Periodontitides" OR "Periodontitides, Periapical" OR "Periodontitis, Periapical" OR "Periodontitis, Apical" OR "Apical Periodontitides" OR "Apical Periodontitis" OR "Periodontitides, Apical" OR "Periodontitis, Acute Nonsuppurative" OR "Acute Nonsuppurative Periodontitides" OR "Acute Nonsuppurative Periodontitis" OR "Nonsuppurative Periodontitides, Acute" OR "Nonsuppurative Periodontitis, Acute" OR "Periodontitides, Acute Nonsuppurative"))	204
	#2	(#2=("Calcium compounds" OR "Oxides" OR "Aluminum compounds" OR "Silicates" OR "Calcium Silicate-based Sealer" OR "Resin-based Sealer" OR "Calcium Silicate-based Sealer" OR "Root Canal Sealer"))	
	#3	(#3=("Bismuth" OR "Calcium hydroxide" OR "Epoxy resins" OR "Calcium Hydroxide" OR "Epoxy Resins" OR "Root Canal Filling Material" OR "Root Canal Sealants" OR "Sealants, Root Canal" OR "Canal Sealant, Root" OR "Canal Sealants, Root" OR "Root Canal Sealant" OR "Sealant, Root Canal" OR "Silicate" OR "Calcium Silicate-based Sealer" OR "Resin-based Sealer" OR "Calcium Silicate-based Sealer" OR "Root Canal Sealer")	
	#4	#1 AND #2 AND #3	
SCOPUS	#1	(#1= TITLE-ABS-KEY ("Periapical Periodontitides" OR "Periodontitides, Periapical" OR "Periodontitis, Periapical" OR "Periodontitis, Apical" OR "Apical Periodontitides" OR "Apical Periodontitis" OR "Periodontitides, Apical" OR "Periodontitis, Acute Nonsuppurative" OR "Acute Nonsuppurative Periodontitides" OR "Acute Nonsuppurative Periodontitis" OR "Nonsuppurative Periodontitides, Acute" OR "Nonsuppurative Periodontitis, Acute" OR "Periodontitides, Acute Nonsuppurative"))	229
	#2	(#2= TITLE-ABS-KEY ("Calcium compounds" OR "Oxides" OR "Aluminum compounds" OR "Silicates" OR "Calcium Silicate-based Sealer" OR "Resin-based Sealer" OR "Calcium Silicate-based Sealer" OR "Root Canal Sealer"))	
	#3	(#3= TITLE-ABS-KEY ("Bismuth" OR "Calcium hydroxide" OR "Epoxy resins" OR "Calcium Hydroxide" OR "Epoxy Resins" OR "Root Canal Filling Material" OR "Root Canal Sealants" OR "Sealants, Root Canal" OR "Canal Sealant, Root" OR "Canal Sealants, Root" OR "Root Canal Sealant" OR "Sealant, Root Canal" OR "Silicate" OR "Calcium Silicate-based Sealer" OR "Resin-based Sealer" OR "Calcium Silicate-based Sealer" OR "Root Canal Sealer")	
WEB OF SCIENCE	#1	#1= ("Periapical Periodontitides" OR "Periodontitides, Periapical" OR "Periodontitis, Periapical" OR "Periodontitis, Apical" OR "Apical Periodontitides" OR "Apical Periodontitis" OR "Periodontitides, Apical" OR "Periodontitis, Acute Nonsuppurative" OR "Acute Nonsuppurative Periodontitides" OR "Acute Nonsuppurative Periodontitis" OR "Nonsuppurative Periodontitides, Acute" OR "Nonsuppurative Periodontitis, Acute" OR "Periodontitides, Acute Nonsuppurative")	37
	#2	#2=("Calcium compounds" OR "Oxides" OR "Aluminum compounds" OR "Silicates" OR "Calcium Silicate-based Sealer" OR "Resin-based Sealer" OR "Calcium Silicate-based Sealer" OR "Root Canal Sealer")	
	#3	#3= ("Bismuth" OR "Calcium hydroxide" OR "Epoxy resins" OR "Calcium Hydroxide" OR "Epoxy Resins" OR "Root Canal Filling Material" OR "Root Canal Sealants" OR "Sealants, Root Canal" OR "Canal Sealant, Root" OR "Canal Sealants, Root" OR "Root Canal Sealant" OR "Sealant, Root Canal" OR "Silicate" OR "Calcium Silicate-based Sealer" OR "Resin-based Sealer" OR "Calcium Silicate-based Sealer" OR "Root Canal Sealer")	
EMBASE	#1	#1= ("Periapical Periodontitides" OR "Periodontitides, Periapical" OR "Periodontitis, Periapical" OR "Periodontitis, Apical" OR "Apical Periodontitides" OR "Apical Periodontitis" OR "Periodontitides, Apical" OR "Periodontitis, Acute Nonsuppurative" OR "Acute Nonsuppurative Periodontitides" OR "Acute Nonsuppurative Periodontitis" OR "Nonsuppurative Periodontitides, Acute" OR "Nonsuppurative Periodontitis, Acute" OR "Periodontitides, Acute Nonsuppurative")	20
	#2	#2= ("Calcium compounds" OR "Oxides" OR "Aluminum compounds" OR "Silicates" OR "Calcium Silicate-based Sealer" OR "Resin-based Sealer" OR "Calcium Silicate-based Sealer" OR "Root Canal Sealer")	
	#3	#3= ("Bismuth" OR "Calcium hydroxide" OR "Epoxy resins" OR "Calcium Hydroxide" OR "Epoxy Resins" OR "Root Canal Filling Material" OR "Root Canal Sealants" OR "Sealants, Root Canal" OR "Canal Sealant, Root" OR "Canal Sealants, Root" OR "Root Canal Sealant" OR "Sealant, Root Canal" OR "Silicate" OR "Calcium Silicate-based Sealer" OR "Resin-based Sealer" OR "Calcium Silicate-based Sealer" OR "Root Canal Sealer")	

Table 2. Data extraction of the randomized clinical trials

First author	Study design	Sample size	Duration of follow-up	Number	Age (mean,)	Gender	Inclusion criteria	Exclusion criteria
Graunaite *et al.* [25]	RCT	61 patients, 122 teeth	24 h, 48 h, 72 h and 7 days	AH Plus: 57, Total Fill: 57	49.5 years (mean)	Male: 25 Female: 36	Patients with Asymptomatic apical periodontitis (AAP), 2 single-rooted teeth	Teeth with large periapical lesions, medically compromised, symptomatic teeth, overfilling
Ferreira *et al.* [31]	RCT	57 patients,60 teeth	24 h, 48 h and 7 days	AH Plus: 20, EndoFill: 20, MTA Fillapex: 20	41 years (mean)	Male: 17 Female: 40	Patients with pulp necrosis in anterior teeth and premolars, patients older than 18 years	Teeth with previous endodontic treatment, uncontrolled systemic diseases, or pregnancy, patients with cognitive difficulties
Tan et al. [40]	RCT	160 patients, 163 teeth	1, 3 and 7 days	AH Plus:83, TotalFil:80	21 + Years	Male: 76 Female: 87	Vital, non-vital and previously root-filled teeth meeting	Patient who was pregnant or presented with autoimmune diseases, cracked or unrestorable teeth, teeth with periodontal probing depths 5mm or more, incomplete root formation
Bardini et al. [12]	RCT	42 patients, 69 teeth	1, 3, 6 and 12 months	BioRoot: 23, Pulp Canal Sealer: 19	BioRoot: 53.17 years, Pulp Canal Sealer: 51.26	BIOROOT: 26.09% male, PULP CANAL SEALER: 47.37% male	Permanent teeth with signs/symptoms of endodontic need	Teeth with poor prognosis due to altered root canal morphology, patients immune compromised
Khandelwal et al. [39]	RCT	63 patients	24h, 48h, 72h and 7 days, 1, 3 and 6 months	Tubli-Seal: 21, AH Plus: 21, BioRoot RCS: 21	Tubli-Seal: 41.57, AH Plus: 41.68, BioRoot RCS: 43.63	Tubli-Seal: male 12, female 7; AH Plus: male 15, female 4; BioRoot RCS: male 11, female 8	Patients with tooth diagnosis of necrotic pulp with chronic apical periodontitis, 18-80 years	Patients classified other than ASA -1, immature permanent tooth, tooth exhibiting endodontic-periodontic lesions, dystrophic calcifications within the tooth as well as more than 20°curvature, pregnant or lactating women, root fracture cases, patients who consumed analgesics before 12-24 h prior to the primary root canal treatment
Hu et al. [21]	RCT	61 patients, 76 teeth	6, 12 and 24 months	iRoot SP: 43, AH Plus: 33	33.2 mean (20-73 years)	Male: 11 Female: 50	Primary endodontic treatment, restorable teeth, consent to participate in the study	Patients with immunosuppressive and systemic diseases, age under 18, those with open apices or periodontal diseases

Supreet *et al.* [41]	RCT	40 patients, 40 teeth	24 h, 48 h and 7 days	AH Plus: 20, Nishika BG: 20	AH Plus: 34.95 years, Nishika BG: 33.5 years	Not mentio ned	Patients with necrotic pulp, first/second molars, primary endodontic lesions < 2 mm	Teeth with root fractures, teeth requiring retreatments, teeth with large periapical lesions, patients with primary periodontic and secondary endodontic lesions, systemic diseases, pregnant
Buker *et al.* [42]	RCT	60 patients	3, 5 and 7 days (visual analog scale),6,12, 24 and 48 h (post operative pain)	EndoSeal MTA: 30, Sealapex: 30	20–60 years	Male: 53.3% Female: 46.7%,	Symptomatic apical periodontitis, systemically healthy, pulp sensitivity confirmed	Root resorption, immature teeth, teeth with crown damage, previous root canal sealer, severe malocclusion, recent analgesic use
Alzoubi *et al.* [43]	RCT	194 patients,2 11 teeth	1, 3 and 7 days	SBO: 106 teeth, WVC: 105 teeth	16-65 years	Males:1 10 Females :102	16–65 years of age at the time of recruitment, The ASA physical status classes I or II, no have allergies to any materials used, NSRCT of a permanent tooth with fully formed root was to be performed including incisors, canines, premolars and molars, tooth had to be restorable and without advanced	Pregnancy or current breastfeeding, root resorption, an adjacent tooth also requiring endodontic treatment, immature teeth, history of previous root canal treatment, history of cracked tooth syndrome or trauma, tooth that required a post
Nagpal *et al.* [38]	RCT	90 patients	6 h ,24 h , 48 h, 5 and 7 days	AH Plus: 30, Nishika Canal Sealer BG: 30, Bio-C Sealer Ion+: 30	18–50 years	Not specifie d	Good oral hygiene, individuals in the age range of 18-50, individuals who have not used antibiotics or analgesic in 7 days, extended positive reaction to cold/electric pulp tester, mandibular first/second molars with symptomatic irreversible pulpitis and apical periodontitis, pulp exposed during caries removal bleeding profusely, patients with healthy periapical tissues	Patients with impaired immune system or systemic disorders, advanced periodontal disease, calcification, open apex, resorption, systemic sensitivity/allergies, patients who are pregnant
Pandey *et al.*[44]	RCT	63 patients	24 h, 48 h and 7 days (postprocedural pain); 3 and 6 months (periapical healing)	ZOE: 21, AH Plus: 21, Bioceramic: 21	29.81 years (mean)	Not specifie d	Patients with apical periodontitis, periapical index score ≥2, VAS pain score ≥3	Immature teeth, root fractures, resorption
Nathani *et al.* [34]	RCT	89 patients ,101 teeth	8, 24 and 48 hours	BioRoot™ RCS: 49, AH Plus: 40	18-50 years	Male: 50 Female: 39	Patients with necrotic pulp and apical periodontitis, patients with no relevant oral abnormalities, patients with no systemic diseases	Teeth requiring crown lengthening, teeth with periodontal probing depth > 5mm, teeth with cracks, root fractures or root resorptions, pregnant women

Detailed summary of the randomized clinical trials included in the systematic review. The table presents essential study characteristics such as author and year of publication, country, study design, sample size, randomization and blinding methods, duration of follow-up, demographic data (age and sex), and inclusion and exclusion criteria; RCT: Randomized Clinical Trial

Table 3. Characteristics of primary and secondary outcomes

First author	Used Sealer	PAI	Cicatrization	Pain	Primary outcome	Secondary outcomes	Measurement method	Time points for outcome measurement
Graunaite *et al.* [25]	AH Plus (Dentsply Maillefer), Total Fill (FKG Dentaire)	Evaluated using Orstavik et al. scoring	Not assessed	Assessed via VAS scale at 24h, 48h, 72h, and 7 days	Postoperative pain levels	Not mentioned	VAS scale	24h, 48h, 72h, 7 days
Ferreira *et al.* [31]	AH Plus, EndoFill, MTA Fillapex	Not assessed	Not assessed	Assessed via descriptive pain scale	Postoperative Pain	Analgesic intake	Simple descriptive pain scale	24h, 48h, 7 days
Tan *et al.* [40]	TotalFill BC, AH Plus	Not assessed	Not assessed	Assessed via Fisher's test	Post-obturation pain	Not mentioned	Likert scale ranging (0-5)	Day 1, Day 3, Day 7
Bardini et al. [12]	BioRoot RCS, Pulp Canal Sealer ZOE	Progressive decrease observed	Bioroot: 76.92%, PULP CANAL SEALER: 56.67%	Not assessed	Periapical healing	Tooth survival	PAI scoring, clinical evaluation	1, 3, 6, 12 months
Khandelwal *et al.* [39]	Tubli-Seal, AH Plus, BioRoot RCS	Not assessed	Not assessed	Assessed via Friedman's test	Periapical healing	Post treatment pain reduction	Kolmogorov-Smirnov and Shapiro-Wilk's test, Chi Square test, Mann Whitney U Test	24h, 48h, 72h and 7 days, 1, 3 and 6 months
Hu *et al.* [21]	iRoot SP , AH Plus	Evaluated using Orstavik scoring system	Improvement observed across all groups	Assessed via VAS scale	Clinical success (asymptomatic, functional teeth with PAI ≤ 2)	Radiographic periapical healing	VAS scale, digital radiographs, PAI score	6, 12, and 24 months
Kaur *et al.* [41]	AH Plus (epoxy resin-based), Nishika Canal Sealer BG (bioceramic)	Not assessed	Not assessed	Assessed via Heft-Parker VAS scale	Postoperative pain response	Not mentioned	Heft-Parker VAS scale	24h, 48h, 7 days
Buker *et al.* [42]	EndoSeal MTA (calcium silicate-based), Sealapex (calcium hydroxide-based)	Scores < 2 included	Not assessed	Assessed via VAS scale	Postoperative pain levels	Analgesic intake	VAS scale (0-100mm), clinical follow-up	6h, 12h, 24h, 48h, day 3, day 5, day 7
Alzoubi *et al.* [43]	Calcium silicate-based (CSS), Resin-based sealer (RBS)	Not assessed	Not assessed	Assessed via numeric ranking	Postoperative pain	Analgesic intake	Numeric Rating Scale (NRS)	1 day, 3 days, 7 days
Nagpal *et al.* [38]	AH Plus (epoxy resin-based), Nishika Canal Sealer BG (bioactive glass-based), Bio-C Sealer Ion+ (bioceramic-based)	Not assessed	Not assessed	Assessed via VAS scale	Post-obturation pain levels	Analgesic intake	VAS scale	6h, 24h, 48h, 5 days, 7 days
Pandey *et al.* [44]	ZOE, AH Plus, Meta ceraSeal	Evaluated at baseline, 3 months and 6 months	Improvement observed across all groups	Assessed via VAS scale	Reduction in postoperative pain	Periapical healing	VAS scale, digital radiographs	24h, 48h, 7 days, 3 months, 6 months
Nathani *et al.* [34]	BioRoot™ RCS (calcium silicate-based), AH Plus (resin-based)	Not assessed	Not assessed	Assessed via VAS scale	Postoperative pain levels	Not mentioned	VAS scale	8h, 24h, 48h

Summary of the main findings reported in the included randomized clinical trials. The table describes the irrigation protocols used in each study, the corresponding primary and secondary outcomes, measurement methods, and time points for outcome evaluation. Both control and intervention groups are presented to allow comparison of bacterial reduction and other clinical parameters

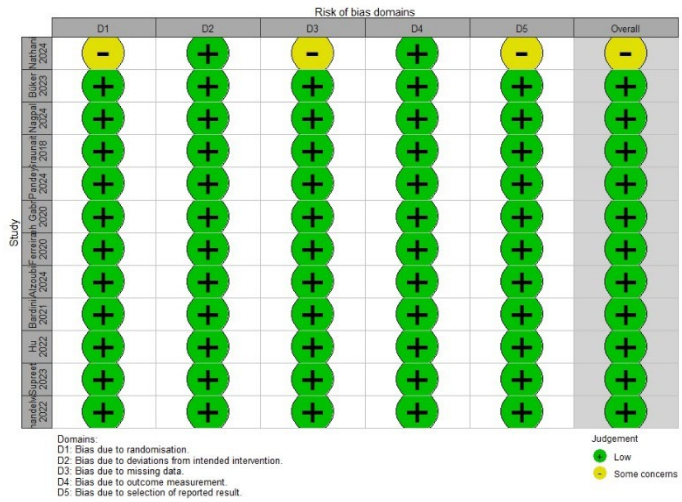

Figure 2. Risk of bias assessment for the included randomized clinical trials (RoB 2.0 tool)

Characteristics of Included Studies: The characteristics of the studies in this systematic review revealed a diverse range of geographical origins, methodologies, and participant profiles. Twelve randomized clinical trials (RCTs) were analyzed, and conducted in Italy, China, Turkey, Brazil, Lithuania, India, Spain, Kuwait, and Singapore, representing a broad spectrum of clinical settings. All studies adhered to a randomized design; the majority of studies employed a single-blind methodology (7 studies), in which only the patient was involved. Four studies utilized a double-blind approach to enhance the reliability of the results by minimizing observer and participant biases. One study did not mention the blinding methodology. Randomization methods were detailed in the randomized clinical trial, with random allocation achieved through a coin toss by a dental assistant, coin flip, MS Excel, GraphPad software, or computerized sequences generated using opaque envelopes, sealed envelopes, and web-based randomization software (random.org). Additionally, stratified computer-generated randomization was implemented in some cases. However, one study did not specify the method of randomization. The total sample size across all included studies is 980 participants. Sample sizes varied from 40 to 194 participants, with patient allocation balanced across intervention and control groups. Follow-up durations demonstrated significant heterogeneity, ranging from evaluations of 24 hours to 24 months. Patient ages varied widely across studies, with broader ranges spanning 17 to 73 years. While the gender distribution was explicitly reported in some studies (11-110 men, 36-102 women) and mentioned as a percentage in others (18%-56.2% men, 43.8%-82% women), three studies did not specify it. The inclusion criteria focused on patients with asymptomatic and symptomatic apical periodontitis (AAP), as well as those with necrotic pulp in anterior teeth, premolars, and first/second molars. Studies targeted single-rooted teeth, permanent teeth exhibiting signs or symptoms of endodontic need, and restorable teeth. Participants were required to provide consent to participate in the study. Eligible patients included those undergoing primary endodontic treatment, individuals aged 16 to 65 years at recruitment, and those classified as ASA physical status I or II without allergies to materials used. The selection also extended to patients with previously root-filled teeth, non-vital, vital teeth, and those with periapical index scores ≥2 or VAS pain scores ≥3. Additional criteria ensured participants had good oral hygiene, no systemic diseases, and no use of antibiotics or analgesics within the last seven days. Candidates for nonsurgical root canal treatment (NSRCT) of permanent teeth with fully formed roots included incisors, canines, premolars, and molars. Specific conditions such as mandibular first/second molars with symptomatic irreversible pulpitis and apical periodontitis, pulp exposure during caries removal with profuse bleeding, and healthy periapical tissues were also considered. This comprehensive inclusion framework ensured the selection of patients without relevant oral abnormalities while maintaining clinical relevance across various dental conditions. Overall, the included studies provide a relevant basis for evaluating the efficacy of bioceramic sealers compared with conventional sealers in patients with apical periodontitis. Although the trials differed in follow-up duration, sample characteristics, and clinical protocols, all were randomized clinical trials. These methodological features support the reliability of the evidence. At the same time, the observed heterogeneity reflects real-world clinical diversity and should be considered when interpreting the generalizability of the findings (Tables 2 & 3).

The characteristics of cement usage protocols in endodontics, outcomes, and measurement methods across the included studies exhibit a high degree of variability, reflecting the diversity of experimental designs in evaluating bioceramics in endodontic obturation

The intervention groups used advanced bioceramic sealers in endodontics, including Total Fill, MTA Fillapex, Total Fill BC, BioRoot RCS, iRoot SP, Nishika Canal Sealer BG, EndoSeal MTA, Calcium Silicate-based CSS, Bio-C Sealer Ion+, and Meta CeraSeal. In contrast, the control groups used a variety of sealers, primarily resin-based materials such as AH Plus and Resin-based Sealer RBS. Additionally, some studies included zinc oxide-eugenol-based sealers like Endofill, Tubli-Seal and Pulp Canal Sealer ZOE, as well as calcium hydroxide-based

alternatives like Sealapex. The most frequently utilized sealer was AH Plus, either alone or in combination with other materials such as ZOE. The primary outcomes evaluated included postoperative pain levels, post-obturation pain, and periapical healing. Additionally, clinical success was assessed, defined as asymptomatic and functional teeth with a Periapical Index (PAI)≤2. Rigorous and well-documented evaluation methods were employed, including the Visual Analog Scale (VAS) to quantify postoperative and post-obturation pain response, as well as radiographic analysis to assess periapical healing. The reduction in postoperative pain was a key parameter, with measurements taken at various time points, ranging from the immediate postoperative period to long-term follow-ups. Secondary outcomes were less frequently reported and not always specified, suggesting a focus on primary endpoints with limited evaluation of other clinical parameters (Table 3).

Among the aspects considered were analgesic intake, tooth survival, and radiographic periapical healing. The heterogeneity in measurement time points, ranging from short-term (*e.g.*, 1 day, 1 week) to longer follow-ups, reflects the complexity of these studies and their attempt to capture both the immediate and sustained effects of the sealers. Overall, the findings highlight the importance of assessing the long-term impact of these materials in endodontics, although variability in protocols and secondary outcomes suggests the need for more systematic studies to draw definitive conclusions. Secondary outcomes were less frequently reported and not always specified, suggesting a focus on primary endpoints with limited evaluation of other clinical parameters.

Post-treatment pain reduction was assessed in multiple studies, although with different methodologies and measurement scales. Overall, a significant reduction in pain was observed in most of both treatment groups, although one trial indicated that pain reduction at day 7 was significantly greater in a specific group. Another study reported low median pain values on the Visual Analog Scale (VAS) on days 1, 3, and 7, with no significant differences between the obturation materials. A study reported higher pain levels at 24 hours with calcium hydroxide-based sealer compared to epoxy resin-based and bioceramic sealers. Additionally, the same study assessed apical healing, demonstrating that the bioceramic sealer exhibited significantly superior repair capacity at 3 and 6 months of evaluation compared to epoxy resin-based and zinc oxide-based sealers. Postoperative complications were scarcely documented, and all studies reported the absence of significant adverse events, reinforcing the safety profile of the materials used in endodontic procedures (Table 4).

In conclusion, the heterogeneity in outcome reporting, particularly in the evaluation of radiographic healing and post-operative pain reduction, underscores the need for standardized protocols to improve comparability between studies and obtain more robust conclusions regarding the efficacy of obturation materials used in endodontics.

Risk of bias assessment

Risk of bias was assessed using the Cochrane RoB 2.0 tool. Overall, 11 of the 12 included randomized controlled trials were judged to be at low risk of bias, while one study was rated as having some concerns. The concerns were identified in the domains related to the randomization process (D1), missing outcome data (D3), and selection of the reported result (D5). All studies were judged to be at low risk of bias for deviations from intended interventions (D2) and measurement of the outcome (D4). These findings indicate that the included trials were generally of high methodological quality, supporting the internal validity of the synthesized results.

Meta-analysis results

Of the twelve studies identified and included in the qualitative synthesis, only four met the methodological and statistical criteria required for inclusion in the quantitative meta-analysis. In accordance with established methodological standards (PRISMA guidelines and the Cochrane Handbook for Systematic Reviews of Interventions), studies were eligible for meta-analysis only if they reported extractable and comparable quantitative outcome data. The remaining eight studies were excluded from the meta-analysis due to the absence of sufficient statistical information, including missing variance measures, lack of group-wise stratification of outcomes, or inconsistent reporting formats.

The eight studies excluded from the quantitative synthesis were not excluded from the systematic review, but only from the meta-analysis. The main reason was that these trials primarily reported postoperative pain outcomes using VAS, NRS, or descriptive pain scales, without providing extractable dichotomous event data for periapical healing. Specifically, Graunaite *et al.* [25], Ferreira *et al.* [31], Tan *et al.* [40], Kaur/Supreet *et al.* [41, 45], Buker *et al.* [42], Alzoubi *et al.* [43], Nagpal *et al.* [38], and Nathani *et al.* [34]lacked comparable group-wise healing event data required for pooled risk ratio estimation. The specific reasons for exclusion from the meta-analysis are provided in Supplementary Table 1.

Quantitative synthesis was performed using Review Manager 5.4 and R (meta package). A random-effects model (DerSimonian–Laird) estimated pooled risk ratios (RRs) with 95% CIs. Heterogeneity was assessed using I^2, τ^2, and Cochran's Q test; $P<0.05$ was considered statistically significant. Publication bias was evaluated with funnel plots.

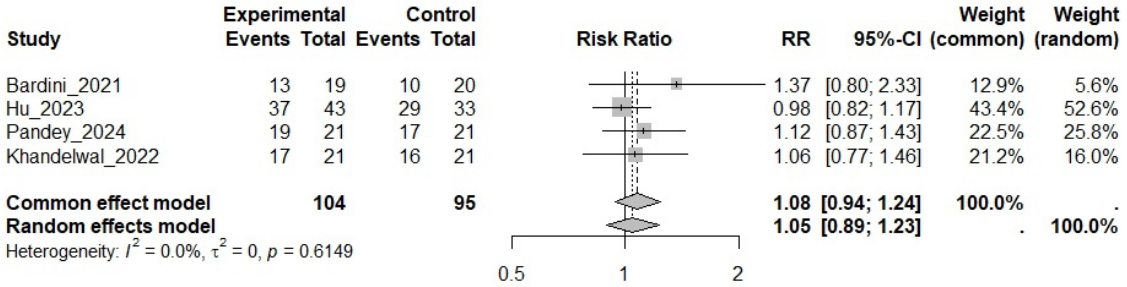

Figure 3. Forest plot comparing periapical healing rates between bioceramic and conventional sealers

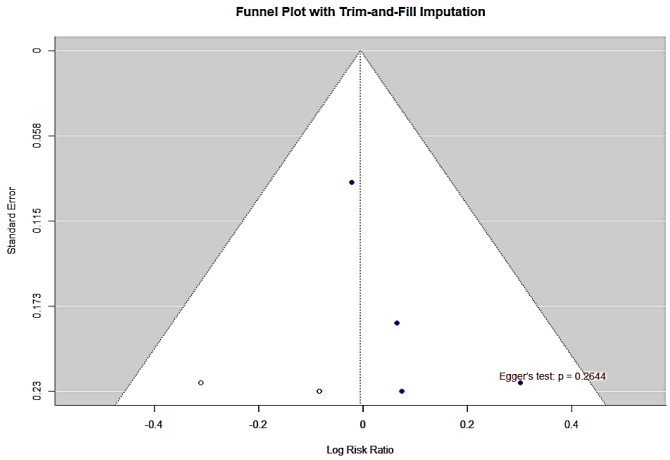

Figure 4. Funnel plot assessing the relationship between effect size and standard error. Egger's regression test indicated no statistically significant asymmetry (z=1.12, *P*=0.2644)

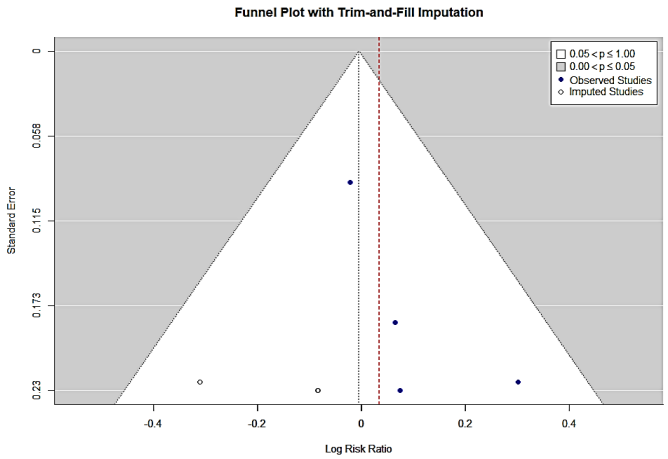

Figure 5. Funnel plot with trim-and-fill imputation. Two missing studies were imputed on the left side. The adjusted pooled estimate (RR=0.995, 95% CI: -0.1333 to 0.1237) was consistent with the original, suggesting minimal publication bias

Four RCTs Bardini *et al.* [12], Hu *et al.* [21], Pandey *et al.* [44], and Khandelwal *et al.* [39] met the inclusion criteria and were included in the quantitative synthesis. All studies compared periapical healing outcomes between bioceramic and conventional root-canal sealers over follow-up periods ranging from 6 to 12 months.

The pooled random-effects estimate indicated no statistically significant difference in healing success between the two groups (RR=1.05, 95% CI 0.89-1.23, *P*=0.6149). The common-effect (fixed-effect) model produced a comparable result (RR=1.08, 95% CI 0.94-1.24). The common-effect (fixed-effect) model produced a comparable result (RR=1.08, 95% CI 0.94-1.24). Heterogeneity was negligible (I^2=0%, τ^2=0), demonstrating strong methodological consistency across trials.

Although the point estimate slightly favored bioceramic sealers, the confidence interval encompassed unity, confirming no statistically discernible superiority between materials (Fig. 3).

A funnel plot was generated to assess potential publication bias (Fig. 4). Although slight asymmetry was observed, Egger's regression test did not indicate statistically significant asymmetry (z=1.12, *P*=0.2644). A trim and fill analysis estimated two potentially missing studies on the left side of the funnel plot (Fig. 5). After imputing these studies, the adjusted pooled effect size remained consistent with the original estimate RR=0.995 (95% CI: 0.875 to 1.132) indicating minimal risk of publication bias. These results should be interpreted cautiously given the limited number of studies included in the meta-analysis (n=4).

The pooled random-effects estimate (RR=1.05 [95% CI: 0.89-1.23]) shows no significant difference between materials, with no heterogeneity detected (I^2=0%, τ^2=0, *P*=0.6149). The diamond represents the overall effect size, positioned close to the line of no effect, indicating comparable clinical outcomes between both sealer types.

A leave-one-out sensitivity analysis showed that the overall effect size remained stable across iterations, indicating robustness of the pooled estimate.

These findings suggest that both sealers achieve comparable clinical efficacy regarding periapical tissue repair. A leave-one-out sensitivity analysis showed consistent pooled effect estimates, indicating robust findings despite the limited number of trials.

Table 4. Characteristics of other outcome

First author	Success criteria	Bacterial load before and after treatment	Periapical lesion size	Healing rate based on radiographs	Reduction in post-treatment pain	Postoperative pain (VAS score)	Complications
Graunaite *et al.* [25]	Reduction in postoperative pain	Not discussed	Not assessed	Not assessed	Observed in both groups	No significant difference between groups	No significant complications reported
Ferreira *et al.* [31]	Reduction in postoperative pain	Not discussed	Not assessed	Not assessed	Pain significantly reduced by day 7	Not significant differences between groups (P>0.05)	None significant
Tan *et al.* [40]	Reduction in postoperative pain	Not discussed	Not mentioned	Not measured	Pain was mild and similar among the 2-sealer group	Day 1: median 1, Day 3: median 1, Day 7: median 2	None reported
Bardini *et al.* [12]	PAI < 2, no symptoms	Not discussed	Reduction in PAI scores over time	BIOROOT: 67.86%, PULP CANAL SEALER: 50%	Not discussed	Not discussed	No major complications reported
Khandelwal *et al.* [39]	Reduction of size of lesion and reduction in pain	Not discussed	Reduction observed in radiographs	Not assessed	No difference in the mean pain score between the groups at any of the time intervals	Tubli-Seal group have the highest pain score followed by AH Plus and BioRoot RCS at 24 to 48 h and gradually declined at 7 d	No significant complications reported
Hu *et al.* [21]	Asymptomatic, functional teeth with PAI ≤ 2	Not discussed	Reduction observed in radiographs	iRoot SP: 85%, AH Plus: 88.2%	Both groups showed reduction in pain	No significant difference between groups	No significant complications reported
Kaur *et al.* [41]	Reduction in postoperative pain	Not discussed	Not assessed	Not assessed	Significant reduction at 24h, no significant differences at 48h and 7 days	Significant at 24h (P=0.022), not significant at 48h or 7 days (P>0.05)	No significant complications reported
Buker *et al.* [42]	Reduction in postoperative pain	Not discussed	Not assessed	Not discussed	Both groups showed reduction in pain	No significant difference between groups	No significant complications reported
Alzoubi *et al.* [43]	Reduction in postoperative pain	Not discussed	Not assessed	Not discussed	No significant differences in post-operative pain	1 day: 1.8, 3 days: 0.8, 7 days: 0.3	No significant complications reported
Nagpal *et al.* [38]	Reduction in postoperative pain	Not discussed	Not assessed	Not evaluated	Bio-C Sealer Ion+ showed least pain, followed by Nishika Canal Sealer BG, then AH Plus at all the time intervals	Significant differences at 6h and 24h (P<0.05), no significant differences beyond 48h,5 day or 7 days	None significant
Pandey *et al.* [44]	Reduction in pain and periapical lesion size	Not discussed	Reduction observed in follow-ups	Not specified	Notable reduction observed	No significant difference among groups	No significant complications reported
Nathani *et al.* [34]	Reduction in postoperative pain	Not discussed	Not assessed	Not evaluated	Similar levels observed for both sealers	No significant difference between groups (P>0.05)	None significant

Summary of additional clinical outcomes reported in the included randomized clinical trials. The table presents information regarding periapical lesion size, radiographic healing rate, reduction in post-treatment and postoperative pain (VAS or NRS scores), and reported complications. These secondary outcomes complement the main findings on bacterial reduction and root canal disinfection efficacy

Interpretation: The present meta-analysis, which synthesized data from four randomized clinical trials involving 380 participants, found no statistically significant difference in periapical healing rates between bioceramic and conventional root canal sealers.

These findings suggest clinical equivalence between these materials in terms of tissue repair outcomes. Although bioceramic sealers are often promoted for their bioactivity and favorable handling characteristics, this meta-analysis demonstrates that such theoretical advantages do not necessarily translate into superior clinical outcomes regarding periapical healing. This highlights the importance of evidence-based material selection grounded in patient-centered outcomes.

Meta-analysis of postoperative pain was not performed due to substantial heterogeneity in measurement tools, follow-up durations, and incomplete reporting across included studies.

Discussion

This systematic review and meta-analysis included 12 randomized clinical trials (RCTs) comparing the efficacy of bioceramic sealers versus conventional sealers in endodontic treatment of apical periodontitis. The following clinical outcomes were evaluated: periapical healing, postoperative pain reduction, and safety (adverse events).

Four studies [12, 21, 25, 34] assessed periapical healing using periapical radiographs and the PAI index. Bardini *et al.* [12] reported a healing rate of 67.86% in the BioRoot RCS group compared to 50% with Pulp Canal Sealer, suggesting a potential advantage of bioceramic sealers. However, this result was not statistically significant (P=0.0735), limiting the certainty of the evidence. Similarly, Pandy *et al.* [44] compared iRoot SP with AH Plus and reported healing rates of 85% and 88.2%, respectively, with no significant differences (P>0.05). These findings align with those of Graunaite *et al.* [25], who found no clear clinical advantage between Total Fill and AH Plus regarding radiographic healing.

Notably, Khandelwal *et al.* [39] provided moderate to high-quality evidence showing that BioRoot RCS resulted in statistically significant periapical healing compared to AH Plus and Tubli-Seal. They reported a reduction in apical lesion area from 6.27 mm^2 at 3 months to 13.41 mm^2 at 6 months (P<0.05), suggesting superior osteoinductive potential and biocompatibility of the bioceramic material.

Although some studies suggest a favorable trend toward bioceramic sealers, the overall certainty of evidence remains moderate due to variability in follow-up periods (ranging from 6 to 24 months) and inconsistent methodologies for evaluating healing.

Postoperative pain was assessed in all studies using the Visual Analogue Scale (VAS) at different post-treatment intervals (24 h, 48 h, 7 days). Studies by Ferreira *et al.* [31], Tan *et al.* [40], and Graunaite *et al.* [25] found comparable pain reduction in both groups, with no statistically significant differences (P>0.05). For instance, Tan *et al.* [40] reported median VAS scores of 1, 1, and 2 on days 1, 3, and 7, respectively, with no clear differences between sealers [32].

However, Ferreira *et al.* [31] reported significantly lower pain at day 7 in the bioceramic sealer group. While this findingsuggests a possible advantage, its clinical impact remains uncertain since other studies did not replicate this result. Due to inconsistencies across studies and potential bias in pain assessment (*e.g.*, insufficient blinding), the certainty of evidence is rated as low to moderate.

Five studies [25, 32, 33, 36, 39] reported no significant adverse events, suggesting a comparable safety profile for both sealers. Tan *et al.* [40], Nathani *et al.* [34], and Kaur *et al.* [45] explicitly mentioned the absence of complications in all groups, while other studies did not report adverse effects in detail.

Bioceramic sealers, such as Endosequence BC, have demonstrated lower cytotoxicity and genotoxicity compared to traditional sealers like AH Plus, indicating better biocompatibility with human tissues [42]. However, the limited documentation of adverse events in the included trials restricts a comprehensive assessment of long-term safety.

First, the bioactive potential of these materials is largely contingent on direct contact with periapical tissues, which may be limited in most clinical scenarios where sealer extrusion does not occur. Second, the biological effects observed in vitro (e.g., cell proliferation and mineral deposition) require controlled conditions that differ substantially from the complex in vivo environment of root canal systems. Third, the included RCTs exhibited variations in clinical protocols, such as obturation technique, irrigation regimen, and follow-up duration, all of which may attenuate the expression of the material's biological properties.

Consequently, while bioceramic sealers offer promising theoretical and biological benefits, current evidence suggests that these advantages do not consistently translate into superior clinical outcomes in the context of periapical healing or postoperative pain reduction. This highlights the multifactorial nature of endodontic success, where factors such as canal disinfection, apical sealing, and operator skill may play a more decisive role than the choice of sealer material itself.

Several previous studies have explored the impact of bioceramic sealers on periapical healing, reporting promising outcomes such as 100% lesion healing or improvement at 6 months [40, 46]. Nonetheless, head-to-head comparisons with conventional sealers have not demonstrated clear superiority [47]. This aligns with findings from Pandy *et al.* [44], where iRoot SP and AH Plus showed healing rates of 85% and 88.2%, respectively (P> 0.05).

In this review, Nathani *et al.* [34] and Pandey *et al.* [44] found a slight reduction in PAI scores with BioRoot RCS compared to AH Plus, though not clinically significant. Conversely, Khandelwal *et al.* [39] reported a statistically significant improvement in periapical healing with BioRoot RCS over both AH Plus (epoxy resin-based) and Tubli-Seal (calcium hydroxide-based) at 3 and 6 months.

Literature suggests that instrumentation technique and apical sealing have a more pronounced effect on postoperative inflammation than the choice of obturation material [35, 36]. Studies by Büküer *et al.* [42], Alzoubi *et al.* [43], and Tan *et al.* [40]using the VAS showed progressive pain reduction in both groups, with no significant differences at 24 h, 48 h, or 7 days. These results are consistent with Graunaite *et al.* [25], who also found no faster pain reduction with bioceramic sealers compared to AH Plus.

However, Ferreira *et al.* [31] reported that patients treated with BioRoot RCS experienced faster pain relief at day 7 (P<0.05), a result not corroborated by other studies. This suggests that postoperative pain differences may be more related to treatment technique than the sealer used.

This systematic review demonstrates several methodological strengths. Chief among them is the exclusive inclusion of RCTs, minimizing bias and enhancing the internal validity of findings. The literature search spanned high-impact databases such as PubMed, Scopus, Web of Science, and Embase, ensuring comprehensive coverage.

Studies like those by Pandy *et al.* [44] and Nagpal *et al.* [38] employed computer-generated randomization and blinded outcome assessment, reducing measurement bias. Furthermore, the inclusion of diverse methodologies and clinical contexts offers a broader perspective on sealer performance across settings.

Despite its strengths, this review has some limitations: clinical heterogeneity: follow-up periods ranged from 7 days [40] to 24 months [41, 48], complicating direct comparison of outcomes, lack of assessor blinding: some studies, such as Nathani *et al.* [34], did not specify whether radiographic assessors were blinded, potentially affecting objectivity,limited safety assessment: most studies did not document adverse events in detail, hindering long-term safety evaluation.

A key limitation of the quantitative synthesis is that only four studies met the criteria for inclusion in the meta-analysis. This small number of studies reduces the statistical power to detect subtle effects and limits the generalizability of the pooled estimate. Additionally, with fewer than ten studies, assessment of publication bias using funnel plots remains unreliable. Therefore, these findings should be interpreted with caution until further high-quality, standardized RCTs provide stronger evidence.

The findings suggest that the choice of sealer should depend more on clinician preference and material availability than on confirmed differences in efficacy. Supreet *et al.* [41, 45] and Nagpal *et al.* [38] concluded that long-term sealer stability remains uncertain and that endodontic success is more dependent on treatment technique than on the sealer itself. Additionally, Pandey *et al.* [44] and Nathani *et al.* [34] noted that bioceramic sealers are more expensive, which may not justify their routine use in resource-limited settings.

Future studies should focus on long-term follow-up (≥5 years) with rigorous methodological control to assess: long-term sealing stability, standardized radiographic assessment (preferably CBCT over conventional radiographs), comparative performance of newer generations of bioceramic sealers.

Conclusions

This systematic review and meta-analysis found no compelling evidence that bioceramic sealers are clinically superior to conventional sealers in promoting periapical healing or reducing postoperative pain in patients undergoing endodontic treatment for apical periodontitis. While bioceramic sealers promise favorable biological properties such as biocompatibility, sustained alkaline pH, and calcium ion release these theoretical advantages have not consistently translated into significant clinical improvements in randomized controlled trials.

The overall quality of evidence remains low to moderate, largely due to heterogeneity in study designs, short follow-up periods, and inconsistent reporting of adverse events. Based on current evidence, the choice of sealer should be informed by handling characteristics, clinician experience, and material availability, rather than assumptions of clinical superiority.

Future high-quality RCTs with extended follow-up durations, standardized radiographic methods (e.g., CBCT), and consistent outcome reporting are essential to determine the long-term clinical efficacy of bioceramic sealers compared to established alternatives.

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Authors' contributions
Conceptualization: MMI/MGGG; Methodology: MMI/MGGG; Formal Analysis and Investigation: /RMPMMMI/MGGG; Writing-Original Draft Preparation: RMPM/MMI; Writing-Review and Editing: MMI/MGGG; Supervision: MMI/MGGG. All authors read and approved the final manuscript.

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Supplementary Table 1. Reasons for exclusion from the quantitative meta-analysis

Study	Main outcome reported	Reason for exclusion from meta-analysis
Graunaite *et al.* [25]	Postoperative pain	Did not report extractable dichotomous data on periapical healing suitable for pooled RR estimation.
Ferreira *et al.* [31]	Postoperative pain	Reported postoperative pain outcomes only; no comparable periapical healing event data were available.
Tan *et al.* [40]	Post-obturation pain	Outcome assessment focused on postoperative pain; healing outcomes were not reported in a format suitable for meta-analysis.
Kaur/Supreet *et al.* [41, 45]	Postoperative pain	Reported pain outcomes without extractable group-wise periapical healing data.
Buker *et al.* [42]	Postoperative pain	Reported pain and analgesic intake outcomes; no comparable periapical healing event data were available.
Alzoubi *et al.* [43]	Postoperative pain	Reported postoperative pain outcomes only; no extractable healing event data were available.
Nagpal *et al.* [38]	Post-obturation pain	Reported pain outcomes using VAS; no comparable periapical healing event data were available.
Nathani *et al.* [34]	Postoperative pain	Reported short-term postoperative pain outcomes only; no extractable periapical healing data were available.