Received: 23 December 2023 | Accepted: 25 March 2024

DOI: 10.1111/iej.14069

INTERNATIONAL ENDODONTIC JOURNAL | WILEY

REVIEW ARTICLE

The efficacy of premixed bioceramic sealers versus standard sealers on root canal treatment outcome, extrusion rate and post-obturation pain: A systematic review and meta-analysis

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Abstract

Background: Limited evidence is available regarding the superior clinical properties of bioceramic sealers comparted with traditional standard sealers.

Objectives: This review aimed to answer the following research questions: 'In healthy patients requiring a root canal treatment (P), what is the efficacy of premixed bioceramic sealers (I) compared with traditional root canal epoxy resin-based sealers (C) in terms of survival, success rates (PICO1) sealer extrusion and resorption (PICO2) post-obturation pain (PICO3) (O)?'

Methods: Authors independently searched three electronic databases: PubMed (including MEDLINE), Web of Science, Embase and Scopus up to 31 October 2023. This was accompanied by both grey literature and manual search. Detailed selection criteria were applied, namely mature permanent teeth requiring root canal treatment, premixed bioceramic sealer with gutta-percha as an intervention group, a standard filling technique as control group and full-text available in English. A random-effect meta-analysis was used to synthesize the body of evidence regarding the use of bioceramic sealers in root canal treatment and their impact on post-obturation pain. Effect sizes were represented as relative risks on a logarithmic scale for binary outcomes and as mean differences for continuous outcomes.

Results: A total of 941 articles were identified. Fifteen Comparative clinical studies were finally included. Eleven were randomized clinical trials, and four were prospective clinical trials with control group. The follow-up of these studies was not greater than 2 years. No publication bias was observed in any study. No significant differences were observed between the two groups in terms of survival and success rates. A small non-significant lower risk of extrusion was observed for bioceramics. A small, non-significantly lower post-operative-pain within 24-h was observed when bioceramics were used.

Discussion: The majority of current evidence shows inconsistencies in reporting and is of short-term duration. Robust prospective long-term trials are needed in this area to better support future recommendations.

Conclusion: This systematic review is the first to analyse several clinical outcomes using premixed sealers. Included studies differed in terms of clinical protocol and operator expertise, but reported a similar outcome when comparing bioceramic versus standard sealers. Tooth survival, treatment outcome, post-operative pain and periapical extrusion were similar and presented no significant differences between the two sealer types.

Registration: PROSPERO database (CRD42023449151).

KEYWORDS

bioactive CaSi, CaSi sealers, meta-analysis, outcome, post-operative pain, premixed bioceramics

INTRODUCTION

The clinical use of premixed root canal sealers has recently increased among endodontic specialists and general dental practitioners, as evidenced by a large number of studies in this area (Camilleri et al., 2022; Cardinali & Camilleri, 2023; Donnermeyer et al., 2019; Primus et al., 2019, 2022). These root canal sealers, incorporate one or more 'bioactive' agents (i.e., Calcium Silicates [CaSi]), radiopacifiers and thickening agents and are commonly categorized under the generic description of a 'bioceramic.'

Recent reviews have proposed several classifications for bioceramic sealers (Camilleri et al., 2022; Donnermeyer et al., 2019; Primus et al., 2022) based upon their clinical use or inherent percentage of bioactive CaSi (Camilleri, 2020; Cardinali & Camilleri, 2023; Primus et al., 2022). The varying percentages of CaSi in bioceramic materials confer different chemical, physical and biological properties, as demonstrated in a number of in vitro (Candeiro et al., 2012; Elsayed et al., 2021; Kharouf et al., 2020; Lee et al., 2017; Souza et al., 2023; Zamparini et al., 2022) and ex vivo biological investigations on human dental and other stem cell populations (Giacomino et al., 2019; López-García et al., 2020; Lozano-Guillén et al., 2022).

However, bioceramic sealers can also be categorized in relation to their composition and formulation, namely as powder liquid, paste to paste or premixed 'ready to use' materials (Camilleri et al., 2022; Cardinali & Camilleri, 2023; Primus et al., 2022). The sealer formulation and 'ready to use' properties have gained particular clinical attention and popularity, but can be problematic in relation to setting time and the lack of a completely set material. The percentage and types of radiopacifiers may also influence their appearance in the root canal and periapical area radiographically (Camilleri & Gandolfi, 2010).

Despite the promising attributes of these bioceramic sealer materials, they have been criticized in relation specifically to their extended setting time and higher in vitro solubility. Setting time of these materials uniquely begins upon contact with moisture, which is distinct from traditional sealers which undergo a catalyst and base setting reaction (Camilleri 2020; Prati & Gandolfi, 2015; Primus et al., 2022). As a result, the complete setting of bioceramics is controversial, and the most suitable level of moisture has still not been reported. This may affect the use of these sealers in the clinic.

Clinical applications of premixed bioceramics were traditionally limited to cold obturation techniques. A single gutta-percha single cone in combination with bioceramic sealers in a cold compaction technique is the most common application. Nevertheless, recent research has provided support for their application in warm obturation techniques, further expanding their potential in root canal treatment procedures (Camilleri et al., 2022).

Clinically, some studies show a radiographic resorption of apically extruded sealers (Chybowski et al., 2018; Spinelli et al., 2023; Zamparini et al., 2023). However, studies to date have a low sample size and do not allow robust conclusions to be made. The relative impact of bioceramic sealers on treatment outcomes, post-operative pain and their dimensional stability when apically extruded remain inconsistent in the literature and as a result, consensus regarding the clinical superiority of premixed bioceramic sealers over traditional resin-based sealers is lacking.

Epoxy resin-based sealers in combination with a heated filling technique have been widely considered 'gold standard' among standard obturation materials (Jasrasaria et al., 2023; Lee et al., 2017; McMichen et al., 2003; Zhou et al., 2013). The use of these materials is supported by robust clinical evidence that a stable seal is formed in a dry root canal, with healing rates ranging from 81 to 96% after at least 5 years follow-up (Chu et al., 2005; Demirci & Caliskan, 2016; Pirani et al., 2019). The presence of moisture in the periapical area and apical reaches of the root canal system

could represent a clinical contraindication that prevents the formation of a stable seal (Jasrasaria et al., 2023; Ørstavik, 2005). Large apical extrusions of resin-based sealers can also be problematic as the free resin exerts a cytotoxic effect before setting completely (Giacomino et al., 2019; Jung et al., 2018).

This systematic review and meta-analysis aimed to critically evaluate the current literature on the use of premixed bioceramic sealers in root canal treatment procedures. By analysing the available clinical investigations, a further objective of this review identify the advantages and the limits of premixed bioceramic sealers in comparison to standard resin-based sealers.

METHODS

This systematic review was conducted in line with Preferred Reporting Items for Systematic Reviews and Meta Analyses (PRISMA) guidelines (Page et al., 2021). The review protocol was registered in the PROSPERO database (CRD42023449151).

The objectives of the systematic review and meta-analysis are summarized in these three PICO review questions:

- (PICO 1) In healthy human patients requiring a root canal treatment (P), what is the effectiveness of premixed bioceramic sealers (I) compared with traditional root canal sealers (C) in terms of survival and success rates (O)?
- (PICO 2) In healthy human patients requiring a root canal treatment (P), what is the effectiveness of premixed bioceramic sealers (I) compared with traditional root canal sealers (C) in terms of periapical sealer extrusion and resorption (O)?
- (PICO 3) In healthy human patients requiring a root canal treatment (P), what is the effectiveness of premixed bioceramic sealers (I) compared with traditional root canal sealers (C) in terms of post-obturation pain (O)?

Inclusion criteria

Articles were selected according the following inclusion criteria:

- *Participants/population*: Mature permanent teeth that required root canal treatment.
- *Intervention*: Non-surgical root canal treatment obturated with a premixed bioceramic sealer in combination with gutta-percha.
- *Comparison*: Non-surgical root canal treatment obturated with a traditional epoxy resin-based sealer in combination with gutta-percha.
- *Study design*: Comparative clinical studies (CCT) reporting the root canal filling protocol and information regarding patient-related and tooth-related characteristics.
- *Language*: Studies were included if they were published as a full article in English and were carried out in a Hospital or University setting.
- *Primary outcomes*: Studies reporting outcomes (survival, success, extrusion rate and occurrence of post-operative pain) using at least one premixed bioceramic sealer.

Exclusion criteria

- Laboratory studies.
- Clinical studies using traditional hydraulic CaSi cements (powder liquid, paste to paste).
- Abstracts only.
- Only protocols.
- Non comparative clinical trials (NCCT).

Outcome measures

PICO 1 (survival and success rates)

- Survival rate: number of teeth still functional at the end of the study period.
- Success rate of root canal treatment: number of teeth with an absence of a periapical radiolucency (Periapical Index, PAI, Strindberg criteria or similar) on radiograph was considered as success in accordance to the methodology used (Periapical radiographs or Cone Beam Computerized Tomography) (strict criteria). Alternatively, the presence of an asymptomatic, reducing in size periapical radiolucency was considered as healing status (studies with a follow-up of less than 4 years). In studies with a longer follow-up, the presence of an asymptomatic periapical radiolucency was defined as not-healed and the tooth was considered as functional (success in accordance to the loose criteria).

PICO 2 (sealer extrusion rate and resorption frequency)

Extrusion and apical sealer resorption were recorded when described in the studies in accordance to the methodology used (Periapical radiographs or Cone Beam Computerized Tomography). The amount of material extruded and its radiographic modification were recorded.

PICO 3 (post-operative pain)

The incidence and intensity of post-obturation pain was recorded according to the methodology used (Visual Analogical Scale [VAS], Likert scale or similar). Pain was analysed at two different end-points, namely immediately after obturation (post-obturation pain; within 1 day) or with the first week after filling (delayed pain; 3 days–7 days).

Data extraction

Two independent reviewers screened the retrieved studies (F.Z, A.S), assessed their eligibility based on the inclusion criteria and extracted data using a standardized data extraction template. The following data were screened: name of the first author, year published, name of the journal, type of study design, the total number of participants, age distribution, type of teeth, number of participants with AP/pulpitis, follow-up period, recall rate, pulp diagnosis, clinical approach, evaluated outcomes and measures employed. Source of fundings was also screened in the studies in accordance to the AMSTAR 2 criteria (Shea et al., 2017). In case of incomplete or missing information, the corresponding author of the papers has been contacted for clarification. Any discrepancies were resolved through discussion or consultation with a third reviewer (C.P.).

Assessment of methodological quality of the included studies

The methodology used for the quality assessment was based on a critical appraisal of the included studies, performed depending on the type of study: for randomized control trials, Cochrane tool for critical appraisal (RoB2) (https://methods.cochrane.org/bias/resources/rob-2-revised-cochrane-risk-bias-tool-randomized-trials) was used, while for controlled clinical trials (non-randomized) a modified version of the Downs and Black checklist (Downs & Black, 1998; Van Raath et al., 2020) was used. The methodological quality of each study was independently scored by two reviewers (F.Z. and A.S.).

RoB2 allowed the methodological assessment of prospective clinical studies. Six domains (D) were analysed, that is (D1. Randomization process, D2. Deviations from intended interventions, D3. Missing outcome data, D4. Measurement of the outcome, D5. Selection of the reported result, D6. Overall Bias). The risk of bias was assessed with three different scores, namely high risk of bias (red circle), some concerns (yellow circle) or low risk of bias (green circle).

The Downs and Black checklist included a total of 27 questions within several criteria: reporting (questions 1–10), external validity (questions 11–13), internal validity – bias (questions 14–20), internal validity (questions 21–26) and power (question 27). The maximum score was 25 for non-randomized comparative clinical studies and 28 for randomized clinical studies. In accordance with previous publications, studies were classified as excellent (26–28), good (20–25), fair (15–19) and poor (≤14) quality (Van Raath et al., 2020).

Information sources

A comprehensive search was made in three electronic databases supplemented by a hand search using a combination of relevant keywords and MeSH terms related to 'root canal treatment' and 'endodontic sealers'. Electronic searches were conducted by two independent reviewers (F.Z. and A.S) using Web of Science, PubMed (MEDLINE) and Scopus (Table S1). Hand searches were performed in the reference lists of included papers and previously published reviews in several top scored journals, including *International Endodontic Journal*, *Journal of Endodontics*, *Australian Endodontic Journal* and *Clinical Oral Investigations*. Additionally, grey literature search was performed (https://opengrey.eu/; https://scholar.google.com/; https://www.greynet.org/; https://clinicaltrials.gov/, https://www.isrctn.com/). The search was restricted to studies published in English. Data search included all studies from 2007 (introduction of the first premixed bioceramic sealer) to October 2023.

Reviewers were trained and calibrated at the start by performing a 'test' literature research with a different number of keywords several times in order to check if comparable hits resulted. All files screened in the study were stored using a reference management program (Mendeley, Mendeley Corporation) and in an Excel spreadsheet. Duplicates were manually removed.

Statistical analysis

A random-effects meta-analysis was conducted to investigate the body of evidence regarding the use of premixed bioceramic sealers in root canal treatments and their impact on post-obturation pain. Effect sizes were represented as relative risks (risk ratios) on a logarithmic scale for binary outcomes and as mean differences for continuous outcomes, with each accompanied by 95% confidence intervals (CIs). All meta-analysis models were estimated using the restricted maximum likelihood (REML) method. The extent of between-study variation in the effect sizes was

assessed using the I^2 statistic, which quantifies the proportion of variation across studies attributed to heterogeneity rather than random chance. Statistical significance of this heterogeneity was evaluated through the Q test. In our investigation for potential publication bias, we utilized the Egger regression-based test. All analyses were conducted using Stata 18 (StataCorp, 2023). The significance level was set at 5%, with the exception of the Q test, for which a 10% significance level was employed due to its limited power when dealing with a small number of studies (Berman & Parker, 2002). Other outcomes relating to survival and extrusion were not suitable for meta-analysis due to heterogeneity of the included studies.

Grading of recommendations assessment, development and evaluation (GRADE)

The certainty of the body of evidence for each evaluated outcome was assessed using Grading of Recommendation Assessment, Development and Evaluation (GRADE) and classified into four categories: high, moderate, low and very low (Goldet & Howick, 2013; Guyatt et al., 2008). Observational studies started at a low level of evidence, (randomized trials from high level) and from here were rated up or down based on serious or very serious concerns in any of the following five domains: risk of bias, the directness of the evidence, the consistency of the results, the precision of the estimates and the risk of publication bias within the included studies.

RESULTS

Study selection

A total of 941 articles were identified from Scopus, Web of Science, PubMed databases and from Gray literature sites and databases (Figure S1). Of these, duplicate studies ($n=200$), conference papers ($n=4$) and non-clinical investigations ($n=606$) were removed. Of these, 14 were removed as they were non-comparative clinical trials (NCC) (case reports or case series), 13 studies were incomplete (study protocols or studies enrolling patients), 26 did not evaluate root canal treatments (i.e., they analysed root end filling, pulp capping, irrigation procedures or post-endodontic techniques), and 51 did not analyse CaSi sealers. In the next stage, a total of 27 full-text articles were assessed for eligibility. After manuscript evaluation, a total of 10 papers were not included because they focused on non-premixed CaSi sealers, namely BioRoot RCS ($n=4$) (Bardini et al., 2021; Khandelwal et al., 2022; Bel Haj Salah et al., 2021; Zavattini et al., 2022), MTA Fillapex ($n=2$) (Coşar et al., 2023; Ferreira et al., 2020), Pro Root MTA ($n=1$) (Thakur et al., 2013), Neo MTA ($n=1$) (Walsh et al., 2023) or Nishika BG ($n=1$) a Bioglass-containing paste to paste sealer (Supreet et al., 2023). One study was excluded due to the presence of a premixed sealer with no specified composition (no SDS was reported) associated with a polymer based obturation system (polyamide core with an outer bonded hydrophilic polymer) (Nagar et al., 2018).

Two additional studies were not included as had no control group (Chybowski et al., 2018; Li et al., 2022) (Table S2). The final evaluation included 15 studies and a total of 1751 patients. The following premixed sealers were included: Endosequence BC (Brasseler, Savannah, USA), also referred as I Root, (Innovative Bioceramix, Vancouver, Canada) or TotalFill BC (FKG Dentaire, Le Chaux-de-fonds, Switzerland), AH Plus Bioceramic sealer, also referred as Endoseal (Maruchi, Gangwon, South Korea) or Endoseal MTA (Maruchi, Gangwon, South Korea), Ceraseal (Meta Biomed, Cheongju-si, South Korea), Bio-C Sealer (Angelus, Londrina, Brasil) and Sealer Plus BC (MK Life, Porto Alegre, Brazil). Control group was constituted of AH Plus (Dentsply, Baillegues, Switzerland), AD Seal (Meta Biomed, Cheongju-si, South Korea) and Bioroot RCS (Septodont, St Maur de Fosses, France).

Study characteristics

Clinical studies analysing PICO 1 (survival and success rates)

Six studies were evaluated (Gautam et al., 2022; Hu et al., 2022; Kim et al., 2021; Pontoriero et al., 2023; Song et al., 2022; Zamparini et al., 2023). Of these, three were randomized clinical studies (Hu et al., 2022; Kim et al., 2021; Song et al., 2022), and three were prospective non-randomized cohort studies (Gautam et al., 2022; Pontoriero et al., 2023; Zamparini et al., 2023). All studies had at least one control group, consisting in epoxy resin-based sealers (AH Plus) or a powder-liquid CaSi sealer. With regards to the obturation techniques in the bioceramic group, three studies used a cold technique with a single cone while three studies used a warm technique. Concerning the study follow-up only two studies reached 24 months duration. The other studies had a duration ranging from 3 months to 18 months. One study was analysed at only 6 months due to the presence of a considerable drop-out at 18 months (86% of patients).

The pooled survival rate of teeth filled using a sealer of premixed bioceramic sealers (Endosequence BC, Ceraseal, Endoseal, I Root, AH Plus Bioceramic and Bio-C sealer) ranged between 97.7% and 100%, while the success (clinical and radiographic) rate ranged between 75% to 100%. Similarly, considering the AH Plus epoxy resin based sealer, the pooled survival rate ranged from 97.8 and 100%, while the success rate (loose criteria, percentage of healing plus healed teeth) ranged from 86.2% to 100% (Table 1). The reasons for teeth not surviving were rarely reported (root fractures in one study) (Zamparini et al., 2023).

Clinical studies analysing PICO 2 (sealer extrusion rate and resorption frequency)

A total of eight studies analysed the occurrence of periapical sealer extrusion. All the studies used periapical radiological methods for investigation. All studies were prospective (Drumond et al., 2021; Fonseca et al., 2019; Gautam et al., 2022; Kim et al., 2021; Pontoriero et al., 2023; Shim et al., 2021; Song et al., 2022; Zamparini et al., 2023), and five of these included a randomization of the filling techniques (Drumond et al., 2021; Fonseca et al., 2019; Kim et al., 2021; Shim et al., 2021; Song et al., 2022). A total of five studies used the premixed sealer with a cold single cone technique, while three studies adopted a warm technique in one of the groups.

Apical extrusion of premixed bioceramic sealers ranged from 11.8% to 59.8%, while apical extrusion of controls ranged from 11.8% to 33.3%. Sealer apical resorption/disappearance was reported in 1 study only when considering premixed bioceramics (Ceraseal) (Table 2).

Clinical studies analysing PICO 3 (post-operative pain)

A total of 11 studies were included and analysed (Aslan & Dönmez Özkan, 2021; Atav Ates et al., 2018; Drumond et al., 2021; Fonseca et al., 2019; Ghobashy & Fakhr, 2022; Graunaite et al., 2018; Kim et al., 2021; Shim et al., 2021; Song et al., 2022; Tan et al., 2021; Yu et al., 2021). All studies were prospective with 10 being randomized clinical trials (Aslan & Dönmez Özkan, 2021; Atav Ates et al., 2018; Drumond et al., 2021; Fonseca et al., 2019; Ghobashy & Fakhr, 2022; Graunaite et al., 2018; Kim et al., 2021; Shim et al., 2021; Song et al., 2022; Tan et al., 2021) and one being a prospective cohort study (Yu et al., 2021). A total of six studies used a cold filling technique (single cone) in the premixed bioceramic groups and five a warm filling technique in one of the groups.

Analysis of post-operative pain was performed using VAS ($n = 10$ studies), Numerical rating scare ($n = 1$ study) and Likert Scale ($n = 1$ study). Post-obturation pain was assessed from 6 h to 3 months. Most of the studies reported similar post-operative pain compared with premixed bioceramic sealers (I Root, TotalFill, Sealer Plus BC, Endosequence BC, Bio-C sealer, Endoseal MTA and Ceraseal) and control (AH Plus or ADseal). Interestingly, one study reported less analgesic intake in I Root group when compared with AH Plus group at 72 h (Atav Ates et al., 2018) (Table 3).

Quality assessment

The quality assessment of the randomized clinical study included studies is summarized in Table 4a, while assessment on prospective studies is reported in Table 4b.

The included randomized studies generally had some quality concerns. Only two studies had a low risk of bias in all the investigated domains (Aslan & Dönmez Özkan, 2021; Kim et al., 2021). Six studies had some concerns due to the difficulties of clinically perform the obturation protocol without knowing the material or technique (D2), three studies also revealed a large drop-out or performed the outcome evaluation in a limited portion of the whole samples included in the study (D3) (Drumond et al., 2021; Fonseca et al., 2019; Hu et al., 2022).

With regards to the four prospective investigations included in the analysis, the methodological quality of prospective studies was good/fair for 3 out of 4 studies (Gautam et al., 2022; Yu et al., 2021; Zamparini et al., 2023). One study had a poor score because there existed marked discrepancies between the different obturation groups and patients characteristics were not clearly described (Pontoriero et al., 2023).

Meta analysis

PICO 1 (survival and success rates)

Survival rate

None of the six trials exhibited a significant difference related to tooth survival between the treatment groups (Figure 1). The total overall estimate of the population relative risk on the logarithmic scale was 0.002 (95% CI −0.018 to 0.022), which corresponds to a non-significant relative risk of 1.002 (95% CI 0.982

TABLE 1 Clinical studies analysing PICO 1 (tooth survival and success rates).

Reference	Study	*N*	Filling technique	Premixed sealer	Control	Follow-up	Final survival	Final success (% of healed + healing)	Healed	Healing
Song et al. (2022)	RCT	16/18/17/20	Single cone	Ceraseal, Endoseal	AH Plus ADseal	1 week, 1 month, 3 months	100% Ceraseal 100% Endoseal 100% AH Plus 100% ADseal	87% Ceraseal 75% Endoseal 86% AH Plus 80% ADseal	87% Ceraseal 75% Endoseal 86% AH Plus 80% ADseal	Not reported
Hu et al. (2022)	RCT	43/33	Warm vertical compaction	I Root	AH Plus	6,12,24 months	97.7% I root 100% AH Plus	85% I root 88.2% AH Plus	Not reported	Not reported
Kim et al. (2021)	RCT	35/39	Sealer-based obturation Continuous wave obturation technique	Endoseal MTA	AH Plus	6–29 months follow -up	100% Endoseal MTA 100% AH Plus	94.3% Endoseal MTA 92.3% AH Plus	71.4% Endoseal MTA 51.3% AH Plus	22.9% Endoseal MTA 41% AH Plus
Gautam et al. (2022)	Prosp	50/50	Single cone technique, Warm vertical compaction	Ceraseal	AH Plus	6–18 months follow-up	100% Ceraseal 100% AH Plus	100% Ceraseal 100% AH Plus	70% Ceraseal 48% AH Plus	30.0% Ceraseal 52% AH Plus
Pontoriero et al. (2023)	Prosp	115/35/20/40	Warm condensation, carrier based	Ceraseal, AH Plus Bio, Bio-C Sealer	Bioroot RCS	Minimum 18 months	100%	99.1 Ceraseal 97.5% Ah Plus Bio 100% Bio-C sealer 100% Bioroot RCS	83.5% Ceraseal 70% AH plus Bio 65% Bio-C sealer 48.6% Bioroot RCS	15.6% Ceraseal 27.5% AH plus Bio 35% Bio-C sealer 51.4% Bioroot RCS
Zamparini et al. (2023)	Prosp	45/44	Carrier-based	Ceraseal	AH Plus	6, 12, 24 months	97.8% Ceraseal 97.8% AH Plus	97.8% Ceraseal 97.8% AH Plus	91.1% Ceraseal 88.6% AH Plus	6.8% Ceraseal 9.2% AH Plus

TABLE 2 Clinical studies analysing PICO 2 (sealer extrusion rate and resorption frequency).

Reference	Study	*N*	Filling technique	Premixed sealer	Control	Follow-up	Extrusion	Resorption
Fonseca et al. (2019)	RCT	32/32	Single cone	Sealer plus BC	AH Plus	24, 48, 72 h, 1 week	59.8% Sealer Plus 28.18% AH Plus	Not reported
Drumond et al. (2021)	RCT	110/110/110	Warm vertical compaction	Endosequence BC, Bio-C sealer	AH Plus	6, 12, 24, 48 h and 1 week	11.8% AH Plus 11.8% Endosequence BC 11.8% Bio-C sealer	Not reported
Shim et al. (2021)	RCT	35/32	Single cone, Warm continuous wave technique	EndoSeal MTA	AH Plus	7 days	14.2% Endoseal MTA 25% AH Plus	Not reported
Kim et al. (2021)	RCT	35/39	Sealer-based obturation Warm continuous wave obturation technique	Endoseal MTA	AH Plus	6–29 months follow - up	28.6% Endoseal MTA 41.0% AH Plus	Not reported
Song et al. (2022)	RCT	16/18/17/20	Single cone	Ceraseal, Endoseal	AH Plus ADseal	1 week, 1 month, 3 months	29.7% Ceraseal 17.8% Endoseal 33.3% AH Plus 12.2% ADseal	Not reported
Gautam et al. (2022)	Prosp	50/50	Single cone technique, Warm vertical compaction	Ceraseal	AH Plus	6–18 months follow-up	12.0% Ceraseal 36.0% AH Plus	Not reported
Pontoriero et al. (2023)	Prosp	115/35/20/40	Warm condensation, Carrier-based	Ceraseal, AH Plus Bio, Bio-C sealer	Bioroot RCS	Minimum 18 months	Overall, 40.5% of extrusions was reported (85/210)	Not reported
Zamparini et al. (2023)	Prosp	45/44	Carrier-based	Ceraseal	AH Plus	6, 12, 24 months	13.3% Ceraseal 25% AH Plus	6.8% Ceraseal radiographically resorbed 0% AH Plus

TABLE 3 Clinical studies analysing PICO 3 (post-operative pain).

Reference	Study	*N*	Filling technique	Premixed sealer	Control	Follow-up	Pain assessment	Conclusions
Graunaite et al. (2018)	RCT	61/61	Warm condensation	Total Fill	AH Plus	24, 48, 72 h, 7 days	VAS	Similar intensity of post-op pain
Atav Ates et al. (2018)	RCT	39/39	Carrier-based (Soft core)	I Root SP	AH Plus	6, 12, 24, 72 h	VAS and Huskisson scale	I Root less analgesic intake than ah plus
Drumond et al. (2021)	RCT	13/13/13	Warm vertical compaction	Endosequence BC, Bio-C sealer	AH Plus	6, 12, 24, 48 h and 1 week	VAS	AH Plus and Bio-C showed improvement in pain. No improvement for Endosequence BC
Fonseca et al. (2019)	RCT	32/32	Single cone	Sealer plus BC	AH Plus	24, 48, 72 h and 1 week	VAS	Similar levels of post-op pain
Tan et al. (2021)	RCT	80/83	Single cone	Totalfill BC,	AH Plus	1, 3, 7 days	Likert scale	No differences
Aslan and Donmez Özkan (2021)	RCT	28/30/26	Single cone	Endoseal MTA Endosequence BC	AH Plus	6, 12, 24, 48 h 3–7 days	VAS	No differences
Shim et al. (2021)	RCT	35/35	Single cone, Warm continuous wave technique	EndoSeal MTA	AH Plus	7 days	VAS	Similar post-operative pain values
Yu et al. (2021)	Prosp	41/51	Single cone/warm compaction	Endosequence BC	AH Plus	4, 24, 48 h	NRS (numerical rating scale)	No differences
Song et al. (2022)	RCT	16/18/17/20	Single cone	Ceraseal, Endoseal	AH Plus ADseal	1 week, 1 month, 3 months	VAS	No differences
Kim et al. (2021)	RCT	35/39	Sealer-based obturation Warm continuous wave obturation technique	Endoseal MTA	AH Plus	6–29 months follow-up (mean 17 months)	VAS	No differences in pain distribution among groups
Ghobashy & Fakhr (2022)	RCT	50/50	Single cone / lateral condensation	Endosequence BC	AH Plus	6, 12, 48 h and 1 week	VAS	Lower post-operative pain for premixed sealer group (but no significant differences)

TABLE 4 (a) Modified Down and Black checklist for assessment of methodological quality (Van Raath et al., 2020). (b) Cochrane tool for critical appraisal of included randomized clinical studies.

Reference	Score	Methodological quality
(a)		
Yu et al. (2021)	20	Good
Gautam et al. (2022)	17	Fair
Pontoriero et al. (2023)	10	Poor
Zamparini et al. (2023)	20	Good

(b)

Reference	D1	D2	D3	D4	D5	Overall
Graunaite et al. (2018)	+	!	+	+	!	!
Atav Ates et al. (2018)	+	!	+	+	+	!
Fonseca et al. (2019)	+	+	!	!	+	!
Drumond et al. (2021)	+	+	!	+	!	!
Tan et al. (2021)	+	!	+	+	+	!
Aslan and Donmez Özkan (2021)	+	+	+	+	+	+
Song et al. (2022)	+	+	+	!	!	!
Hu et al. (2022)	!	!	−	+	+	!
Kim et al. (2021)	+	!	+	+	+	+
Shim et al. (2021)	+	+	!	+	!	!
Ghobashy & Fakhr (2022)	+	!	+	+	!	!

to 1.022) in favour of premixed bioceramic sealers (p-value = .83). The p-value from the chi-squared test for homogeneity was .99, indicating that the extent of variation in effect sizes across studies was only due to chance. No publication bias was detected by Egger's test (p-value = .48).

Success rate

None of the six included trials exhibited a significant difference between the groups (Figure 2). The total overall estimate of the population relative risk on the logarithmic scale was 0.014 (95% CI −0.022 to 0.051), which corresponds to a non-significant relative risk of 1.015 (95% CI 0.978 to 1.052) in favour of premixed bioceramic sealers (p-value = .44). The p-value from the chi-squared test for homogeneity was .63, indicating that the extent of variation in effect sizes across studies was only due to chance. No publication bias was detected by Egger's test (p-value = .52).

PICO 2 (sealer extrusion rate and resorption frequency)

One study was not included in the meta-analysis as did not analyse extrusions (Pontoriero et al., 2023). As illustrated in Figure 3, five out of seven trials included in the meta-analysis did not exhibit a significant difference between the treatment groups. In contrast, Fonseca et al. (2019) reported a risk ratio of 2.11 (95% CI 3.94 to 26.46), indicating a significantly higher rate of extrusion among premixed bioceramic sealers (Fonseca et al., 2019), while Gautman et al. (2022) reported a risk ratio of 0.33 (95% CI 0.14 to 0.77), indicating a significantly lower rate among premixed bioceramic sealers (Gautam et al., 2022). The total overall estimate of the population relative risk on the logarithmic scale was −0.182 (95% CI −0.636 to 0.271), which corresponds to a non-significant relative risk of 0.833 (95% CI 0.529 to 1.312) in favour of premixed bioceramic sealers (p-value = .43). However, the

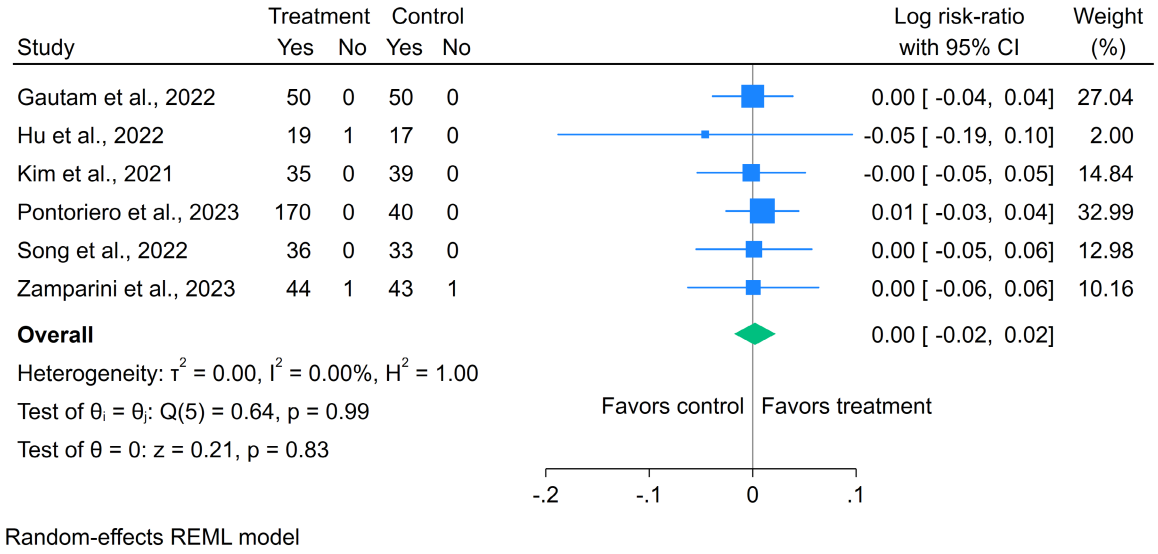

FIGURE 1 Forest plot of trials comparing the effect of premixed bioceramic sealers versus conventional epoxy resin sealers on survival rate. *Note*: The trials included in the meta-analysis are identified on the left side by their principal author and date of publication. For each treatment group, the number of elements that did or did not experience the study outcome is displayed in the columns labelled 'Yes' and 'No'. These data were used to calculate the risk ratio and its 95% confidence interval on a logarithmic scale for each trial, which is presented on the right side of the plot and also graphically represented in the centre. Each trial is represented by a square, and its associated 95% confidence interval is shown as a horizontal line. The size of each square is proportional to the sample size of the trial. The solid vertical line in the centre of the graph represents the 'line of no effect', which corresponds to a risk ratio of 1.0, indicating no difference between the intervention and control groups. The overall estimate of the population relative risk on a logarithmic scale is presented in the row labelled 'Overall'. This estimate is graphically depicted by a diamond shape. The centre of the diamond corresponds to the total overall estimated relative risk, while the ends of the diamond indicate the limits of the 95% confidence interval. The contribution of each trial to the overall estimate is indicated under the heading 'Weight (%)'. The percentage weight assigned to a trial is determined by the precision of its sample estimate for the population parameter. Trials with more precise estimates, indicated by narrower confidence intervals, have a greater weight in the overall estimate.

p-value from the chi-squared test for homogeneity was .01, and the I^2 statistic was 64.6%, indicating substantial heterogeneity and partially unexplained inconsistency across the study results. No publication bias was detected by Egger's test (*p*-value = .08).

PICO 3 (post-operative pain)

Post-operative pain (0–24 h)

Two studies were not included in the meta-analysis of post-operative pain (Kim et al., 2021; Tan et al., 2021): one did not report mean values, only distinguishing between mild, moderate, severe pain (Kim et al., 2021), while the other presented data not suitable for analysis (postoperative pain was not analysed as values) (Tan et al., 2021). As illustrated in Figure 4, only one out of the seven trials exhibited a significant difference between the treatment groups (Ghobashy & Fakhr, 2022). The total overall estimate of the population mean difference was non-significant at −0.11 (95% CI −0.44 to 0.22) in favour of premixed bioceramic sealers (*p*-value = .52). The *p*-value from the chi-squared test for homogeneity was .36, indicating that the extent of variation in effect sizes across studies was only due to chance. No publication bias was detected by Egger's test (*p*-value = .26).

Delayed post-operative pain (3–7 days)

Two studies were not included in the meta-analysis due to unsuitability of the data (null values in both treatment and control groups) (Aslan & Dönmez Özkan, 2021; Shim et al., 2021). An additional study was also excluded as analysed data in a larger follow-up time (3 months) and was therefore not comparable to the established end-point (3-days–1 week) (Song et al., 2022). As illustrated in Figure 5, four out of five trials did not exhibit a significant difference between the treatment groups. In contrast, Fonseca et al. (2019) reported a mean difference of −0.35 (95%CI −0.68 to −0.02), indicating a significantly lower level of pain among patients treated with bioceramic sealers (Fonseca et al., 2019). The total overall estimate of the population mean difference was non-significant at −0.02 (95%CI −0.22 to 0.17) (*p*-value = .81). However, the *p*-value from the chi-squared test for homogeneity was marginally above the threshold of statistical significance (.105), and the I^2 statistic was 53.8%, indicating substantial heterogeneity

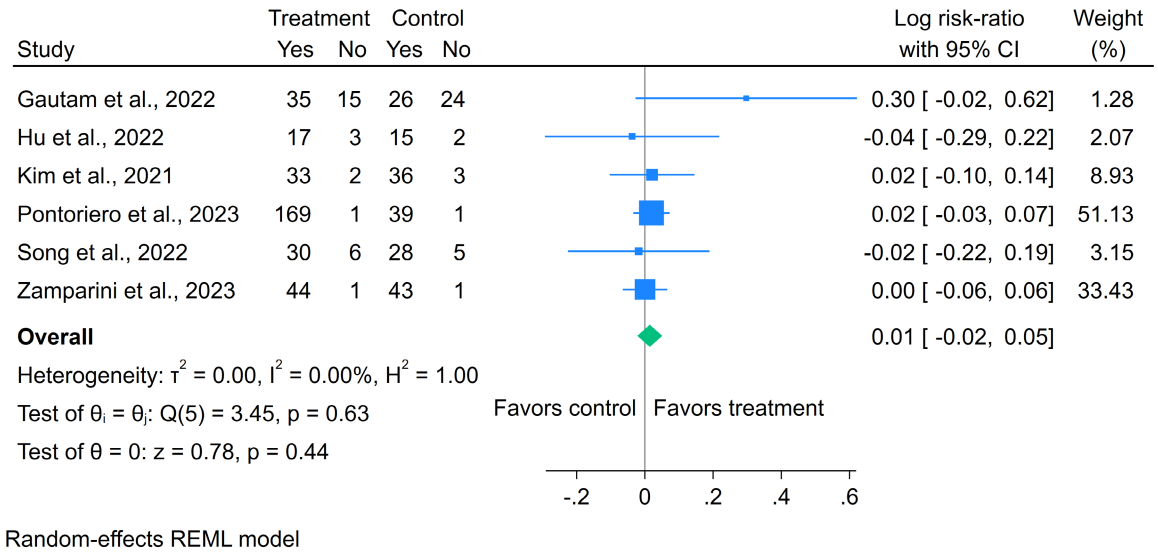

FIGURE 2 Forest plot of trials comparing the effect of premixed bioceramic sealers versus conventional epoxy resin sealers on clinical and radiographic success rate. *Note*: The trials included in the meta-analysis are identified on the left side by their principal author and date of publication. For each treatment group, the number of elements that did or did not experience the study outcome is displayed in the columns labelled 'Yes' and 'No'. These data were used to calculate the risk ratio and its 95% confidence interval on a logarithmic scale for each trial, which is presented on the right side of the plot and also graphically represented in the centre. Each trial is represented by a square, and its associated 95% confidence interval is shown as a horizontal line. The size of each square is proportional to the sample size of the trial. The solid vertical line in the centre of the graph represents the 'line of no effect', which corresponds to a risk ratio of 1.0, indicating no difference between the intervention and control groups. The overall estimate of the population relative risk on a logarithmic scale is presented in the row labelled 'Overall'. This estimate is graphically depicted by a diamond shape. The centre of the diamond corresponds to the total overall estimated relative risk, while the ends of the diamond indicate the limits of the 95% confidence interval. The contribution of each trial to the overall estimate is indicated under the heading 'Weight (%)'. The percentage weight assigned to a trial is determined by the precision of its sample estimate for the population parameter. Trials with more precise estimates, indicated by narrower confidence intervals, have a greater weight in the overall estimate.

and partially unexplained inconsistency across the study results. No publication bias was detected by Egger's test (p-value = .14).

Publication bias

Differences between the clinical protocols and source of fundings

Differences in the clinical protocols among the included studies was described (Table 5). The number of teeth treated with a periapical lesion or a secondary retreatment were more frequent in 7 out of 15 studies. Two studies included only teeth with periapical radiolucency, six studies included teeth with 50% or more teeth with periapical radiolucency, four studies included teeth with less than 50% periapical radiolucency and three studies did not provide information on periapical status.

The type of instrumentation was specified in almost all studies (11 out of 15 studies) and consisted in a NiTi rotary instrumentation (7 out of 11) or a reciprocating NiTi instrumentation (4 out of 11). In the remaining four studies, the operator was able to choose the preferred instrumentation.

The final irrigation rinse and sealer application protocol showed marked differences among the studies. A great heterogeneity on the final irrigation procedures was detected. Final irrigation with only EDTA 17% was performed in two studies, only NaOCl was used in two studies, sterile water was used in three studies, combination of these irrigants was proposed in four studies and no information with final irrigant solution was reported in four cases.

Operator expertise also showed wide variation between studies. Most of the studies were carried out in a University department, with the root canal treatments performed by endodontic specialists (7 out of 15), post-graduate master tutors, operators or endodontic residents (3 out of 15) or private practitioners (2 out of 15). Three of these studies reported a combination of operators. Two studies did not specify the operator expertise.

Source of funding was also evaluated and reported in Table 5. The great majority (11 out of 15 studies) reported no conflicts of interest and no external financial support. Three studies declared a research support from local government

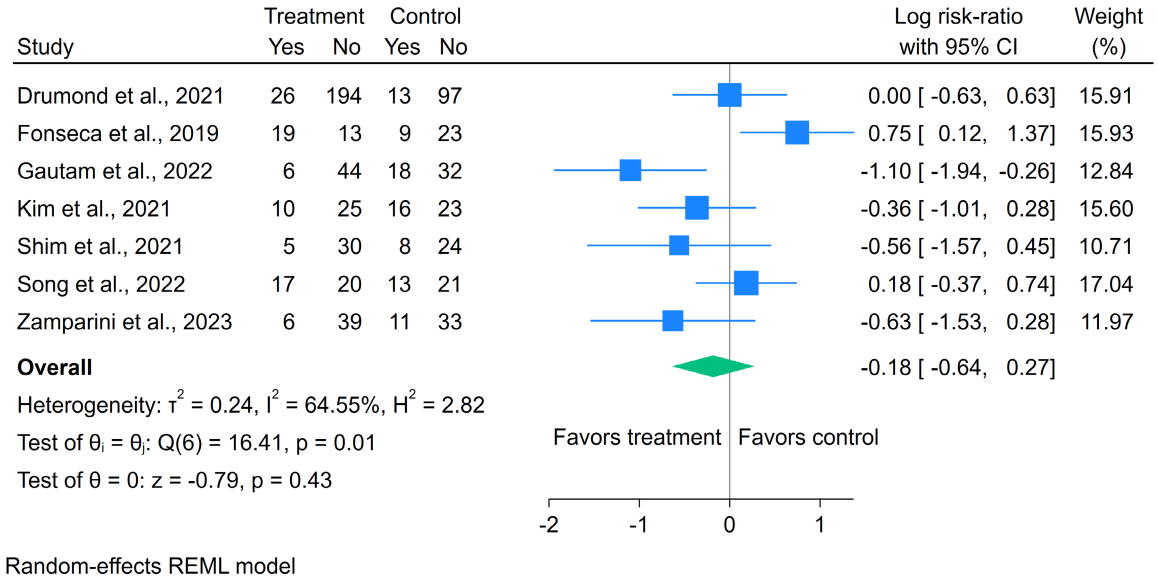

FIGURE 3 Forest plot of trials comparing the effect of premixed bioceramic sealers versus conventional epoxy resin sealers on periapical extrusion rate. *Note*: The trials included in the meta-analysis are identified on the left side by their principal author and date of publication. For each treatment group, the number of elements that did or did not experience the study outcome is displayed in the columns labelled 'Yes' and 'No'. These data were used to calculate the risk ratio and its 95% confidence interval on a logarithmic scale for each trial, which is presented on the right side of the plot and also graphically represented in the centre. Each trial is represented by a square, and its associated 95% confidence interval is shown as a horizontal line. The size of each square is proportional to the sample size of the trial. The solid vertical line in the centre of the graph represents the 'line of no effect', which corresponds to a risk ratio of 1.0, indicating no difference between the intervention and control groups. The overall estimate of the population relative risk on a logarithmic scale is presented in the row labelled 'Overall'. This estimate is graphically depicted by a diamond shape. The centre of the diamond corresponds to the total overall estimated relative risk, while the ends of the diamond indicate the limits of the 95% confidence interval. The contribution of each trial to the overall estimate is indicated under the heading 'Weight (%)'. The percentage weight assigned to a trial is determined by the precision of its sample estimate for the population parameter. Trials with more precise estimates, indicated by narrower confidence intervals, have a greater weight in the overall estimate.

institutions or university scientific grants. One study had one sponsorship with one commercial brand, which granted clinical research materials to perform the investigation.

Grading of recommendations assessment, development and evaluation (GRADE)

GRADE analysis is reported in Tables S3–S5.

The analysis of the root canal treatment outcome (PICO 1) revealed no differences among the two treatments with an overall low certainty of evidence. There was a risk of bias due to high drop-out percentages (Hu et al., 2022; Kim et al., 2021; Song et al., 2022) during follow-up or imprecision (high variability) (Hu et al., 2022) was evident (Table S3).

The analysis of sealer extrusion and resorption (PICO 2) revealed a slightly lower extrusion risk for treatment group (premixed bioceramic sealer). However, the high levels of drop-out (Hu et al., 2022; Kim et al., 2021; Song et al., 2022; Yu et al., 2021) and the indirectness of evidence (sealer extrusion was not the primary outcome in all studies) downgraded the certainty of evidence, which resulted in a low or very low analysis (Table S4).

The analysis of post-obturation pain (PICO 3) revealed a slightly lower post-operative pain for treatment group (premixed bioceramic sealer). Four studies demonstrated high certainty of evidence (Drumond et al., 2021; Fonseca et al., 2019; Graunaite et al., 2018; Song et al., 2022), while four studies were downgraded to moderate evidence due to the increased risk for imprecision due to the high variability rate (Aslan & Dönmez Özkan, 2021; Atav Ates et al., 2018) or high loss to follow-up (Kim et al., 2021; Shim et al., 2021) or increased risk of inconsistency due to not reporting patient-related and tooth-related variables (Ghobashy & Fakhr 2022).

One observational study was downgraded due to the high loss to follow-up (Yu et al., 2021) (Table S5).

DISCUSSION

The present systematic review and meta-analysis aimed to provide an update regarding the strength of clinical

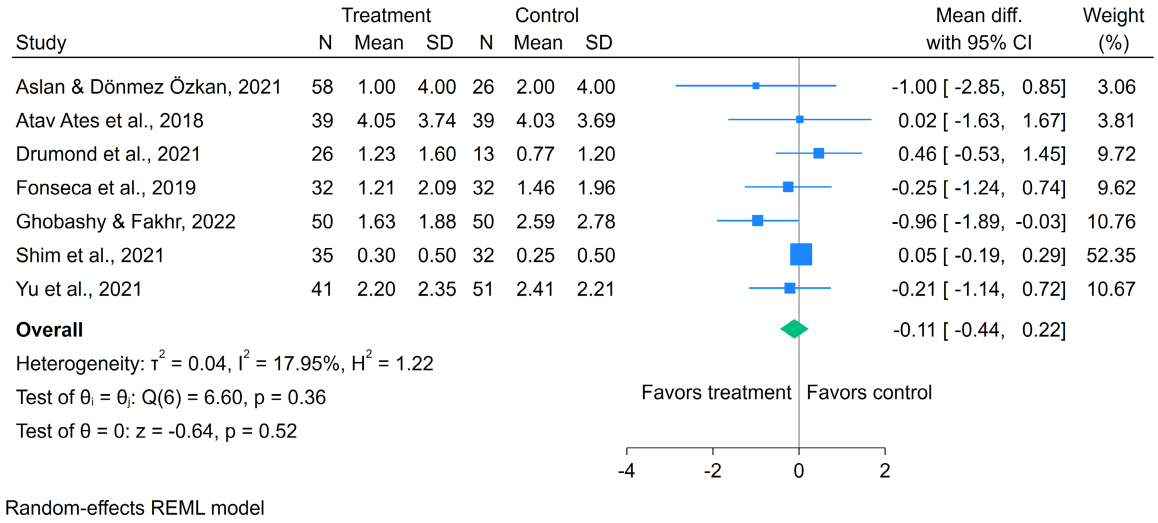

FIGURE 4 Forest plot of trials comparing the effect of premixed bioceramic sealers versus conventional epoxy resin sealers on immediate post-obturation pain. *Note*: The trials included in the meta-analysis are identified on the left side by their principal author(s) and date of publication. For each treatment group, the number of elements, mean and standard deviation (SD) are displayed in the columns labelled 'N', 'Mean' and 'SD'. These data were used to calculate the mean difference and its 95% confidence interval for each trial, which is presented on the right side of the plot and also graphically represented in the centre. Each trial is represented by a square, and its associated 95% confidence interval is shown as a horizontal line. The size of each square is proportional to the sample size of the trial. The solid vertical line in the centre of the graph represents the 'line of no effect', which corresponds to a mean difference of 0.0, indicating no difference between the intervention and control groups. The overall estimate of the population mean difference is presented in the row labelled 'Overall'. This estimate is graphically depicted by a diamond shape. The centre of the diamond corresponds to the total overall estimated mean difference, while the ends of the diamond indicate the limits of the 95% confidence interval. The contribution of each trial to the overall estimate is indicated under the heading 'Weight (%)'. The percentage weight assigned to a trial is determined by the precision of its sample estimate for the population parameter. Trials with more precise estimates, indicated by narrower confidence intervals, have a greater weight in the overall estimate.

evidence on the use of premixed bioceramic sealers used with cold and warm root filling techniques. CaSi based sealers with other formulations, such as Paste to Paste (MTA Fillapex, Endo Fill), powder-liquid (Bioroot RCS, tech Biosealer Endo, NeoMTA Plus) or containing Bioglass (Guttaflow-bioseal or Nishika BG) were not considered in the current review. The reason was to primarily establish the clinical validity of a new material with distinct setting conditions. Finally, one study reporting Smart seal obturation protocol was not included in the meta-analysis. The Smart seal obturation protocol is significantly different from gutta-percha based obturation protocols as they included a polymer based point (polyamide core with an outer bonded hydrophilic polymer) (Nagar et al., 2018). Moreover, no information regarding sealer composition, CaSi content, additive and radiopacifier used is reported in literature and no SDS is available (Cardinali & Camilleri, 2023).The analysis highlighted a limited number of clinical trials on premixed bioceramic sealers, despite the high interest of these materials in endodontics.

The studies included in our review were screened for methodological quality and scientific robustness. The assessment of methodological quality, both in randomized clinical studies and prospective investigations, revealed heterogeneous findings. While some studies demonstrated low risk of bias and good methodological rigour, others raised concerns with difficulties in protocol implementation (particularly in relation to blinding the operator unawareness of the technique used) and high drop-out rates. Additionally, the GRADE analysis highlighted varying levels of certainty across different outcomes, with issues like imprecision and indirectness lowering the quality of evidence. These findings highlight the need for further efforts to pursue a high methodological standard. Improving protocol adherence, minimizing drop-outs and ensuring adequate sample sizes could strengthen the validity and generalizability of future investigations.

The data extracted and analysed were divided and classified according to different clinically relevant outcomes, namely root canal treatment survival and success (PICO 1), occurrence of extrusion (PICO 2) and incidence of post-operative pain (PICO 3).

Recent ESE clinical practice guidelines highlighted the necessity to report both radiographical evidence of apical lesion size modification (loose criteria or healing status) and the radiographic evidence of apical radiolucency disappearance (strict criteria or healed status)

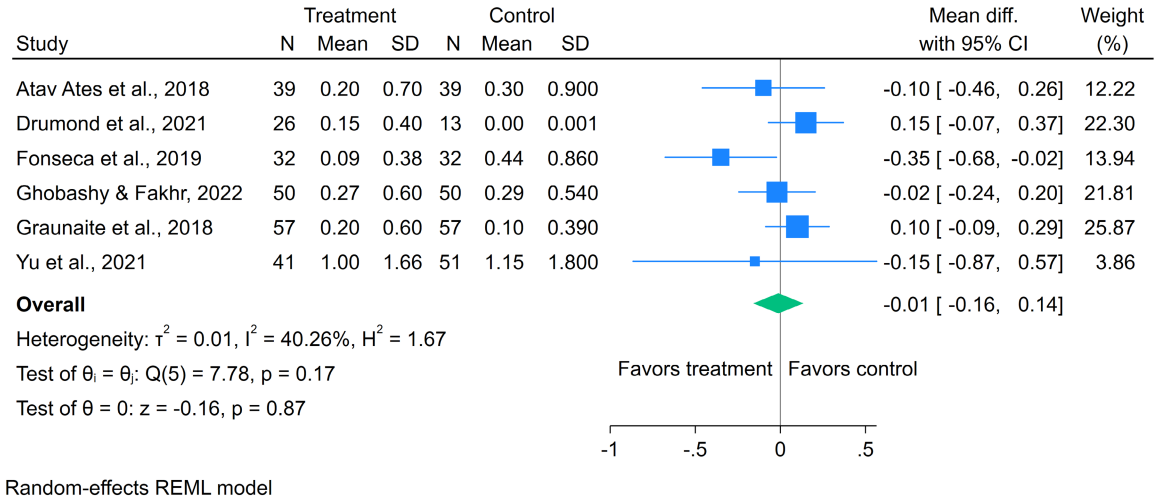

FIGURE 5 Forest plot of trials comparing the effect of premixed bioceramic sealers versus conventional epoxy resin sealers on delayed (1 week) post-obturation pain. *Notes*: The trials included in the meta-analysis are identified on the left side by their principal author(s) and date of publication. For each treatment group, the number of elements, mean and standard deviation (SD) are displayed in the columns labelled '*N*', 'Mean' and 'SD'. These data were used to calculate the mean difference and its 95% confidence interval for each trial, which is presented on the right side of the plot and also graphically represented in the centre. Each trial is represented by a square, and its associated 95% confidence interval is shown as a horizontal line. The size of each square is proportional to the sample size of the trial. The solid vertical line in the centre of the graph represents the 'line of no effect', which corresponds to a mean difference of 0.0, indicating no difference between the intervention and control groups. The overall estimate of the population mean difference is presented in the row labelled 'Overall'. This estimate is graphically depicted by a diamond shape. The centre of the diamond corresponds to the total overall estimated mean difference, while the ends of the diamond indicate the limits of the 95% confidence interval. The contribution of each trial to the overall estimate is indicated under the heading 'Weight (%)'. The percentage weight assigned to a trial is determined by the precision of its sample estimate for the population parameter. Trials with more precise estimates, indicated by narrower confidence intervals, have a greater weight in the overall estimate.

(Duncan et al., 2021, 2023). However, due to the heterogeneous nature of the previously published results and the impossibility in certain cases to obtain the percentages of 'healing' treatments, the meta-analysis evaluated 'loose' criteria.

In our review, an epoxy resin-based sealers (AH Plus) were the most predominant conventional control group. AH Plus is still considered the 'gold standard'. Robust data are evident from the literature are available regarding its use associated principally with warm filling technique (Chu et al., 2005; Demirci & Caliskan, 2016; Pirani et al., 2019). Limitations on the use of epoxy resin-based sealers are that they require a completely dry canal due to marked hydrophobicity (Lee et al., 2017) and their initial cytotoxic activity when incompletely set (Giacomino et al., 2019; Huang et al., 2002; Jung et al., 2018; Kim et al., 2021).

Our review showed statistically similar outcomes in terms of both survival and success/healing rate when premixed bioceramic sealers were compared to epoxy resin sealer. The high percentages of survival rates (97.7% to 100%) did not allow analysis of the cause of failure/extractions. Success rate (loose criteria) showed a greater variation among the evaluated studies and ranged from 75% to 100%.

Interestingly, this trend was confirmed in all studies despite the difference of protocols and professional set-up, including post-graduate master students, endodontic specialists or general practitioners with long clinical expertise. The wide range of success rate could also be attributable to the different distribution of teeth with a periapical lesion or no apical radiolucency or teeth needing a secondary treatment in the included studies. It is widely known that the presence of a root canal infection with an apical radiolucency or a previous root canal treatment induce a considerable drop in root canal success (Gulabivala & Ng, 2023). This data confirms the suitability of premixed bioceramic sealers for a large spectrum of endodontists and clinical situations, but needs to be validated in the long-term.

The occurrence of post-operative pain by subdividing it into post-obturation pain (within 24 h from filling) and delayed post-obturation pain (from 3 to 7 days and more after filling) was analysed. Unexpectedly, the results did not show any significant differences in post-operative pain for both immediate and delayed periods. Interestingly, the data revealed a lower, but non-significant post-operative pain values in the bioceramic sealer group, in particular in the first days after obturation procedures. The reasons could be attributable to

TABLE 5 Comparisons of the included studies with regards of root canal treatments initial diagnosis (number of periapical lesions/total), type of instrumentation, final rinse and sealer application protocol and operator expertise.

Reference	Number of lesions/totals	Type of instrumentation	Final rinse and sealer application protocol	Operator expertise	Source of funding
Graunaite et al. (2018)	The number of teeth with periapical lesion was not reported	Protaper Gold Nickel Titanium (NiTi) instrumentation	Ultrasonic activation of NaOCl 2% and EDTA 17%. Root canals were dried with paper points. Sealer was introduced with a paper point.	Two experienced endodontists	No conflict of interests was declared
Atev Ates et al. (2018)	78/156 teeth (periapical lesions/total)	One Shape NiTi instrumentation	Final irrigation with 5 mL sterile water. Root canal was dried with paper points and sealer was inserted with paper points.	Not reported	Research supported by university research funding
Fonseca et al. (2019)	64/64 teeth (periapical lesions/total)	Reciproc 40/06 single file NiTi instrumentation	Final irrigation of 5 mL NaOCl 2.5%. Root canals were dried with paper points. the sealer was inserted with a lentulo	Not reported	No conflict of interests was declared
Aslan & Dönmez Özkan (2021)	The number of teeth with periapical lesion was not reported	Reciproc 25/08 or Reciproc 40/06 single file NiTi instrumentation	Finally, 3 mL of 17% EDTA, 3 mL of 5% NaOCl and 2 mL of distilled water were used. Root canals were dried with paper points. Sealer was applied with paper point cones	Two endodontic specialists (10 year of practice)	No conflict of interests was declared
Drumond et al. (2021)	The number of teeth with periapical lesion was not reported	Wave One Gold single reciprocating NiTi instrumentation	Final irrigation with 1 mL EDTA 17%. Root canals were dried with paper points.	Endodontic specialist (10 year of practice)	No conflict of interests was declared
Tan et al. (2021)	141/163 (retreatment/total)	NiTi crown down approach, finished with k-files in larger canals	Sealer was carried using a fitted cone in a slow pumping action. No information on the use of paper points or final irrigation protocol.	11 clinicians including endodontic post-graduate students and endodontists	Research supported by the University research grant and sponsorship by FKG Dentaire.
Yu et al. (2021)	31/92 (periapical lesions/total)	Various 0.04 taper nickel titanium up to minimum apical size of 35	Final irrigation not specified. Root canals were dried with paper points. Sealer was injected and spread with lentulo.	Endodontic residents	No conflict of interests was declared
Hu et al. (2022)	47/76 (periapical lesion/total)	Protaper NiTi instrumentation up to F2-F5	Final irrigation with 5 mL 3%NaOCl and 17% EDTA. Root canals were dried with paper points and sealer was introduced with a file.	Endodontic specialist (8 year of practice)	Research supported by regional educational department
Kim et al. (2021)	26/74 (periapical lesion/total)	Preferred operator NiTi instrumentation	Root canal dried with paper points. Sealer dispensed with a 24 G syringe.	6 dentists (5 post-graduate, 1 professor)	No conflict of interests was declared

TABLE 5 (Continued)

Reference	Number of lesions/totals	Type of instrumentation	Final rinse and sealer application protocol	Operator expertise	Source of funding
Song et al. (2022)	31/71 (periapical lesion/total)	Protaper Next NiTi instrumentation	Paper points to dry the canal. Sealer was dispensed through master cone pumping motions	Endodontic specialist (20 year of practice)	No conflict of interests was declared
Shim et al. (2021)	38/70 (periapical lesion/total)	Protaper Next NiTi instrumentation	Final irrigation with NaOCl 5% and water. Root canal dried with paper points. Sealer application protocol not reported	Single practitioner	Research supported by national research funding
Ghobashy & Fakhr (2022)	100/100 (retreatment/total)	Protaper Retreatment up to D3 (20/07) or manual instrumentation	17% EDTA prior to obturation phases. Sealer application protocol not reported.	Two private clinicians	No conflict of interests was declared
Gautam et al. (2022)	40/100 (retreatment/total)	Protaper Universal NiTi up to F2 in primary treatment. Protaper Retreatment up to D1-D3 for secondary treatment	Saline solution as final irrigant. Root canal dried with paper points. Sealer application protocol not reported	One private clinician	No conflict of interests was declared
Pontoriero et al. (2023)	129/210 (periapical lesion/total)	Not reported	Not reported	One endodontic expert operator	No conflict of interests was declared
Zamparini et al. (2023)	49/89 (periapical lesion/total)	M2 or Rotate NiTi instrumentation	Final irrigation with sterile water. Root canals were dried with paper points, sealer introduced with a file.	12 post-graduate master tutors	No conflict of interests was declared

the heterogeneity of the studies, that proposes different root filling techniques. Single cone technique associated with premixed bioceramics sealers was the mostly analysed, in particular when considering post-operative pain. This technique showed similar post-obturation pain values when compared to epoxy resin based sealers and carrier-based techniques (Aslan & Dönmez Özkan, 2021; Fonseca et al., 2019; Song et al., 2022; Tan et al., 2021; Yu et al., 2021).

Finally, periapical extrusion rate was evaluated. This resulted slightly lower for bioceramic sealers when compared to epoxy resin sealers. A previous systematic review revealed that sealer extrusions could have an effect on root canal treatment outcome and post-operative pain incidence (Schaeffer et al., 2005). In contrast, a recent review showed a non-significant correlation between sealer extrusions and root canal treatment outcome (Aminoshariae & Kulild, 2020). Another aim of the study was to analyse if sealer extrusion was more frequent with premixed bioceramic sealers.

The radiographic resorption of premixed bioceramic sealers has been primarily observed by recent investigations (Chybowski et al., 2018; Spinelli et al., 2023; Zamparini et al., 2023). A previous retrospective single-arm study reported that approx. 10% of Endosequence BC extrusions were radiographically undetectable at 36 months follow-up (Chybowski et al., 2018). A recent prospective clinical study reported that half of apically extruded Ceraseal extrusions were radiographically undetectable at 24 months follow-up (Zamparini et al., 2023). The apical extrusion resorption of AH Plus Bioceramic was reported in 50% of total extrusion (Spinelli et al., 2023), highlighting this is a significant problem. The present review confirmed that epoxy resin sealers extrusions were stable with no radiographic modifications or disappearance. Interestingly, a clinical study on powder-liquid CaSi sealers (such as BioRoot RCS) did not observe sealer resorption (Bardini et al., 2021). It is acknowledged that a limitation of this type of research is that it can be difficult, particularly with heated gutta-percha techniques to distinguish the sealer from the obturation material on radiographic analysis. The radiopacity of gutta-percha cones ranged between 7.25 mmAl and 7.53 mmAl (Katz et al., 1990) and some sealers may have a similar radiopacity (TotalFill BC radiopacity was 7.40 mmAl) (Zamparini et al., 2019). However, it should be recalled that other bioceramic sealers radiopacity could be higher (radiopacity of Ceraseal and AH Plus bioceramic sealer was 8.0 mmAl and 8.5 mmAl or more) (Souza et al., 2023; Zamparini et al., 2023) or lower (Neosealer Flo radiopacity was 5.5 mmAl, Endosequence BC Hiflow was 6.1 mmAl) (Zamparini et al., 2023; Zordan-Bronzel et al., 2019). The differences in radiopacity values and extrusion morphology (i.e. apical puff) could help clinicians to distinguish between sealer or gutta-percha extrusions.

The filling technique, apical diameter and operator approach may result in higher or lower apical extrusion (Ricucci et al., 2016). Causes of radiographic sealer resorption are still not well-known as further work is required in this area. It is likely that CaSi sealers (when in contact with bone tissue) could trigger osteoclast cell activity (Hashiguchi et al., 2011) that may induce increased resorption by the body of the periapically extrusion sealer. It has been suggested that apically extruded CaSi could influence the osteoclast/osteoblast metabolisms in a dose-dependent effect during initial stages of the healing of periapical lesions (Rodrigues et al., 2014).

Alternatively, sealer setting time and solubility can create a fast dissolving of extrusion (Prati & Gandolfi, 2015; Primus et al., 2022; Santiago et al., 2021). The combination of Ca and Si release can further increase the porosity and radiodensity of extruded sealer. The apatite nucleation has been widely demonstrated for Ca Si cements (Gandolfi et al., 2010, 2011, 2013; Santiago et al., 2021; Taddei et al., 2009) and confirmed for premixed bioceramic sealers (Lee et al., 2017; Souza et al., 2023; Zamparini et al., 2023).

The analysed sealers had different composition and different radiopacifiers (i.e. Zirconium dioxide, Bismuth oxide or Tantalum pentoxide) and their release from periapical extrusion into the body fluids must be considered in future research. Recent ex vivo studies showed that, upon dissolution of CaSi sealers samples, the radiopacifiers could be spread in the surgical area, taken up by cells and transferred to other organs for their elimination by metabolic processes (de Azevedo Queiroz et al., 2021; Marciano et al., 2023).

Interestingly, although some studies did not comment, most of these studies were performed without any external source of funds. This indicates a minimal influence of external funding sources on the outcomes of the studies included in our meta-analysis. The absence of potential conflict of interest in the vast majority of studies enhances the credibility and reliability of the findings presented in this analysis. This aspect also highlights and confirms the clinical interest in premixed sealers among clinicians and the need to have high quality clinical evidence regarding their use.

The positive outcomes of innovative sealers that are well-documented in the past (Tay & Pashley, 2007), were unfortunately not confirmed in subsequent late investigations (Barborka et al., 2017; Strange et al., 2019). So, caution is advisable regarding the widespread adoption of bioceramic sealers until robust demonstrations supported

by larger-scale studies are available. There is a need for long-term follow-up clinical data on premixed bioceramic sealers to establish their efficacy conclusively.

The meta-analysis allowed the collection and synthesis of the whole available evidence derived from comparative clinical articles published in top-ranked journals, providing a comprehensive and more accurate overview of the current landscape on the effectiveness of bioceramic cements compared to the gold standard. The study has some limitations, including the selection of articles only in English, different study types (randomized and non-randomized CCT), their poor quality and the short-term follow-up period. Our data support the need of further well-designed, long-term studies regarding the occurrence of sealer extrusion and its modification in the periapical area.

CONCLUSIONS

This systematic review highlighted that premixed bioceramic sealers had similar short-term outcomes compared with traditional epoxy resin sealers. It cannot be definitively established if premixed bioceramic sealers have a lower extrusion rate compared with epoxy resin-based sealer or that premixed bioceramic sealers did not exhibit differences in post-operative pain compared with epoxy resin based sealers. This review demonstrated that the bulk of data had limitations in reporting and was of short-term duration. Well planned prospective long-term trials are needed in this area to better support future recommendations.

AUTHOR CONTRIBUTIONS

Conceptualization, C.P.; methodology, F.Z. and J.L.; validation, F.Z., A.S.; formal analysis, J.L.; investigation, F.Z., A.S.; resources, C.P.; data curation, J.L. and F.Z.; writing—original draft preparation, F.Z., C.P., J.L.; writing—review and editing, C.P., M.G.G, H.F.D.; visualization, F.Z., and A.S.; project administration, C.P. and M.G.G. All authors have read and agreed to the published version of the manuscript.

FUNDING INFORMATION

This project did not receive external funding and was supported by the local University.

CONFLICT OF INTEREST STATEMENT

The authors stated no conflicts of interests.

DATA AVAILABILITY STATEMENT

The data that supports the findings of this study are available in the supplementary material of this article.

ETHICS STATEMENT

The study did not require ethical approval.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Zamparini, F., Lenzi, J., Duncan, H.F., Spinelli, A., Gandolfi, M.G. & Prati, C. (2024) The efficacy of premixed bioceramic sealers versus standard sealers on root canal treatment outcome, extrusion rate and post-obturation pain: A systematic review and meta-analysis. *International Endodontic Journal*, 57, 1021–1042. Available from: https://doi.org/10.1111/iej.14069