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POSTOPERATIVE PAIN INCIDENCE AND INTENSITY FOLLOWING ROOT CANAL OBTURATION WITH BIOCERAMIC AND OTHER SEALERS: A SYSTEMATIC REVIEW WITH META-ANALYSIS.

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ABSTRACT

Aims: To investigate whether bioceramic sealers induce a lower incidence and intensity of postoperative pain compared to other sealers.

Materials and Methods: Six electronic databases were searched for studies published up to April 2022, following the PICOS strategy: (P) adult patients undergoing root canal treatment or retreatment; (I) root canal filling using bioceramic sealer; (C) root canal filling using other types of sealers; (O) Primary: postoperative pain incidence and/or intensity; Secondary: number of medication intake; (S) randomized clinical trials. Risk of bias assessment was performed with the revised Cochrane risk of bias tools for randomized trials (RoB 2). Overall certainty of evidence was assessed through the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) tool.

Results: Ten studies were included. Eight studies had a low risk of bias, and two had some concerns risk. Meta-analyses showed no differences regarding postoperative pain intensity and incidence between bioceramic sealers and AH Plus. Number of medication intake seemed to be associated to the preoperative diagnosis. Zinc oxide-eugenol sealer demonstrated an intense postoperative pain compared to bioceramic sealers and AH Plus. GRADE analysis showed a low certainty of evidence for all outcomes.

Conclusions: There seem to be no differences between bioceramic sealers and AH Plus regarding postoperative pain intensity and incidence. Number of medication intake seem to be associated to the preoperative diagnosis. Zinc oxide-eugenol evoked a more pronounced postoperative pain.

KEYWORDS: Bioceramic. Epoxy resin. Zinc oxide-eugenol. Postoperative pain. Systematic review.

INTRODUCTION

Root canal treatment aims to clean, shape and disinfect the root canal system by mechanical and chemical methods enabling to hermetically seal the root canal, and the periradicular tissues to be healed[1,2]. However, even when the root canal treatment is appropriately performed, some patients may experience pain or discomfort postoperatively, which becomes a distressful situation for both clinician and patient[2].

According to the International Association for Study of Pain (IASP), pain is a subjective, unpleasant, emotional and sensory experience associated with actual or potential tissue damage[3]. In endodontics, pain is a common complication within the first 24 hours after the end of treatment, closely related to mechanical, chemical (irrigating solution, intracanal drugs and filling material) and/or microbial factors[2,4].

Postoperative endodontic pain is defined as an unpleasant sensation of any degree of pain, that can occur after the beginning of endodontic

treatment in 3% to 53% of cases, depending on the individual and the variables evaluated[5,6]. The main cause of pain is believed to be the release of inflammatory mediators that activate nociceptors around the tooth by means of substances that cross the apical foramen which can potentially affect the healing process in the periodontal tissues[7].

During obturation, the extrusion of endodontic sealers is a common event. When this extrusion occurs in small amounts, the perirradicular tissues may tolerate the presence of this toxic material[8]. Therefore, root canal sealers with high biocompatibility and high sealing properties are desirable[9].

For these reasons, bioceramic sealers have been gaining acceptance and popularity due to their notable physicochemical and biological properties, such as low cytotoxicity and high biocompatibility[10]. However, despite laboratory studies indicating that these sealers present better biological properties when compared to other endodontic sealers, it is still necessary to evaluate the available literature on pain incidence and intensity promoted by bioceramic sealers compared to other sealers used in clinical practice.

Therefore, this study aimed to answer the following focused question: "Does bioceramic sealers cause a lower incidence and intensity of postoperative pain following obturation when compared to other sealers?"

MATERIALS AND METHODS

The systematic review protocol was registered on the PROSPERO database (CRD42021233551) and was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses PRISMA (http://www.prisma-statement.org)[11] guidelines.

Search strategy

Searches were performed by two examiners (A.T.M. and T.W) independently in the following electronic databases: PubMed/MEDLINE, Cochrane Library, Scopus, Web of Science, EMBASE and Grey Literature Report. Database searches were performed for articles published until April 2022, without year or language restriction.

Table 1. Search strategy in each database.

Database	Search strategy	Findings
PubMed/MEDLINE	#1: Root Canal OR Root Canal Therapy OR Root Canal Treatment OR Endodontics	61.786
	#2: Bioceramic OR Calcium Silicate OR Bioactive Glass	8.814
	#3: Sealer OR Endodontic Sealer OR Epoxy Resin OR Zinc Oxide-Eugenol OR Calcium Hydroxide	20.077
	#4: Pain OR Postoperative Pain OR Postoperative Period	1.103.180
	#1 AND #2 AND #3 AND #4	16
Cochrane Library	#1: Root Canal OR Root Canal Therapy OR Root Canal Treatment OR Endodontics	4.195
	#2: Bioceramic OR Calcium Silicate OR Bioactive Glass	466
	#3: Sealer OR Endodontic Sealer OR Epoxy Resin OR Zinc Oxide-Eugenol OR Calcium Hydroxide	1.655
	#4: Pain OR Postoperative Pain OR Postoperative Period	230.913
	#1 AND #2 AND #3 AND #4	23
Scopus	#1: (ALL (root AND canal) OR ALL (root AND canal AND therapy) OR ALL (root AND canal AND treatment) OR ALL (endodontics))	184.055
	#2: (ALL (bioceramic) OR ALL (calcium AND silicate) OR ALL (bioactive AND glass))	197.992
	#3: (ALL (sealer) OR ALL (endodontic AND sealer) OR ALL (epoxy AND resin) OR ALL (zinc AND oxide-eugenol) OR ALL (calcium AND hydroxide))	331.916
	#4: (ALL (pain) OR ALL (postoperative AND pain) OR ALL (postoperative AND period))	2.769.613
	#1 AND #2 AND #3 AND #4	527
Web of Science	#1: TS=(Root Canal OR Root Canal Therapy OR Root Canal Treatment OR Endodontics)	21.374
	#2: TS=(Bioceramic OR Calcium Silicate OR Bioactive Glass)	26.410

	#3: TS=(Sealer OR Endodontic Sealer OR Epoxy Resin OR Zinc Oxide-Eugenol OR Calcium Hydroxide)	64.693
	#4: TS=(Pain OR Postoperative Pain OR Postoperative Period)	778.473
	#1 AND #2 AND #3 AND #4	12
EMBASE	#1: 'root canal'/exp OR 'root canal' OR (('root'/exp OR root) AND canal) OR (root AND canal AND therapy) OR (root AND canal AND treatment) OR endodontics	64.010
	#2: bioceramic OR (calcium AND silicate) OR (bioactive AND glass)	12.262
	#3: sealer OR (endodontic AND sealer) OR (epoxy AND resin) OR (zinc AND 'oxide eugenol') OR (calcium AND hydroxide)	23.594
	#4: 'pain'/exp OR pain OR (postoperative AND pain) OR (postoperative AND period)	2.231.533
	#1 AND #2 AND #3 AND #4	53
Grey Literature Report	#1: Root Canal OR Root Canal Therapy OR Root Canal Treatment OR Endodontics	0
	#2: Bioceramic OR Calcium Silicate OR Bioactive Glass	0
	#3: Sealer OR Endodontic Sealer OR Epoxy Resin OR Zinc Oxide-Eugenol OR Calcium Hydroxide	0
	#4: Pain OR Postoperative Pain OR Postoperative Period	0
	#1 AND #2 AND #3 AND #4	0

The electronic search strategy was developed using a combination of Medical Subject Heading terms (MeSH) and text words (tw.). The Boolean operators "AND" and "OR" were applied to combine the terms and create a search strategy. The following terms were combined: 'root canal', 'root canal therapy', 'root canal treatment', 'endodontics', 'bioceramic', 'calcium silicate', 'bioactive glass', 'epoxy resin', 'zinc oxide-eugenol', 'calcium hydroxide', 'sealer', 'endodontic sealer', 'pain', 'pain postoperative', 'postoperative period'. Searches in each database and their respective findings are summarized in **Table 1**. Additional manual searches of the reference lists of the selected studies were performed. All articles selected were imported into the Mendeley© (Mendeley Ltd, London, United Kingdom) reference manager to catalogue the references and facilitate the exclusion of duplicates.

Eligibility criteria

The eligibility criteria were based on the PICOS strategy[11-13], as follows:

- P: Adult patients undergoing root canal treatment or retreatment;
- I: Root canal filling using bioceramic sealer;
- C: Root canal filling using other types of sealers;
- O:

  Primary: Postoperative pain incidence and/or intensity;

  Secondary: Number of medication intake to control pain.
- S: Randomized clinical trials.

Only randomized clinical trials that evaluated the postoperative pain of patients submitted to root canal filling with bioceramic sealers comparing to other types of sealers, in root canal treatments or retreatments were included.

Studies that evaluated the use of reparative materials (i.e., mineral trioxide aggregate), animal studies, histological studies, cross-sectional studies, systematic reviews with and without meta-analysis, reviews, letters, opinion articles, conference abstracts, case reports, serial cases and in vitro studies were not included.

Selection of studies

Two independent authors (A.T.M. and T.W.) screened the studies. The first step comprised database search, duplicates removal, and analysis of titles and abstracts. When an appropriate assessment could not be performed by title and abstract, the full text was read for a final decision. The second step comprised full-text assessment of the potentially eligible studies based on the PICOS strategy. Disagreements on study inclusion were solved by discussion with a third author (M.V.R.S.).

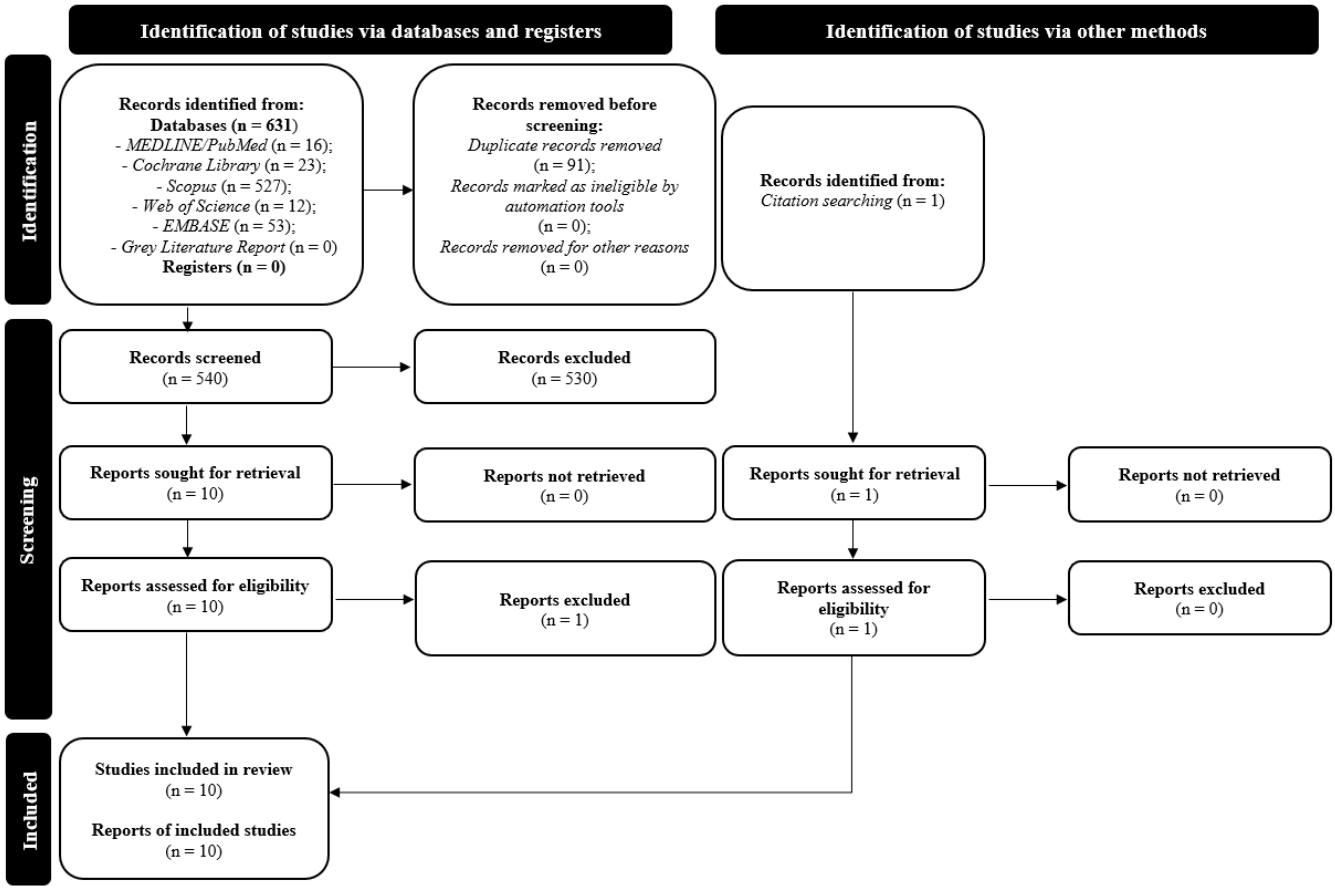


Figure 1. Flow diagram of the systematic literature search according to PRISMA 2020 guidelines.

Data extraction

Data extraction was performed by two authors (A.T.M. and T.W.) independently. Disagreements were solved by a third author (M.V.R.S.). Following data were extracted: author(s) name(s), year of publication, sealers evaluated, participants age, number of treated teeth, teeth included, teeth diagnosis, treatment performed, obturation technique, methods of obturation quality assessment, pharmacological prescription for pain control, methods of postoperative pain assessment, intervals of pain assessment, outcomes and main findings. In case of missing information, the authors were contacted three times by e-mail at an interval of one week.

Assessment of Risk of Bias

Two independent authors (T.W. and A.T.M.) performed the assessment to determine the risk of bias of each study. In case of disagreement, a third author (M.V.R.S.) was consulted.

Assessment of risk of bias was performed according to the Cochrane Risk of Bias tool for randomized controlled trials (RoB 2): 'Bias risk warning from randomized controlled trials' - Cochrane Handbook 6.0[14].

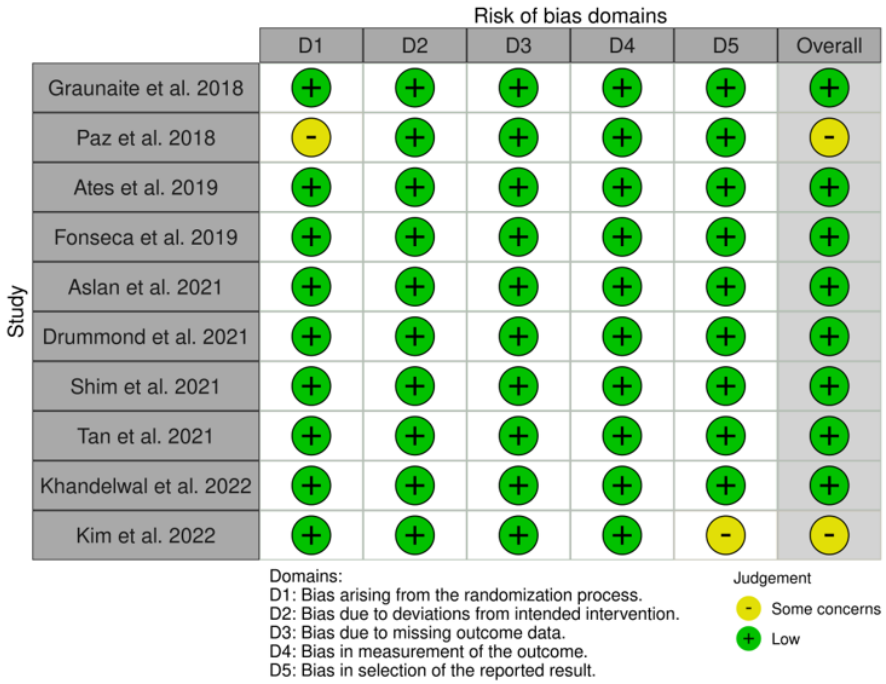
The following domains were considered:

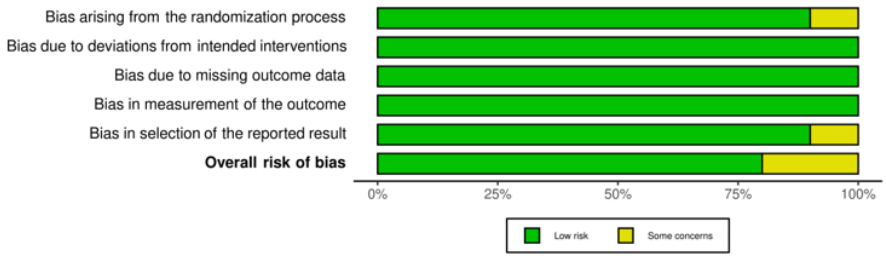
1. Randomization process;
2. Deviations from intended interventions;
3. Missing outcome data;
4. Measurement of the outcome;
5. Selection of reported results.

"Blinding of operators" was not considered since it is not feasible in these types of interventions. Each included study was judged as high risk of bias for negative domain response (red), risk of unclear bias (yellow) when the response was unclear and low risk of bias for positive domain response (green).

In case of missing information, the authors were contacted by e-mail at least three times to obtain more information to allow the studies to be classified as 'low' (green) or 'high' (red) risk of bias. When the information was not possible to be acquired, the articles were classified as unclear risk of bias.

Overall quality was based on scores in individual domains. When a low risk of bias was observed to all domains, the overall quality was of low risk of bias. When at least one domain was of unclear risk, the overall quality was unclear risk of bias. In addition, when at least one domain was set as a high risk or at least three domains were set as with unclear risk, an overall quality of high risk of bias was attributed.





Meta-analysis

The software Review Manager (RevMan - Version 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014) was used for performing meta-analyses. The studies included for quantitative analysis should contain the following information: (1) same periods of assessment; (2) data on the number of events of postoperative pain (incidence); (3) data on mean and standard deviation of postoperative pain (intensity); (4) data on the number of medication intake; (5) same method (scale) of pain evaluation. Meta-analyses were planned for post operative pain intensity, incidence (number of events) and need for medication intake.

Heterogeneity was calculated using the T2, Cochran Q test and I^2 statistics. An I^2 statistic below 30% was considered as not important, between 30% and 60% was considered as moderate heterogeneity, between 50% and 90% as substantial heterogeneity, and over 75% was considered as considerable heterogeneity[15,16]. Random-effect models were adopted for all meta-analyses, due to the methodological heterogeneity of the studies[16]. A P-value of less than 5% was considered significant.

Sensitivity analysis

Additional meta-analyses were planned to explore the influence of: (1) symptomatic teeth; (2) asymptomatic teeth; (3) vital teeth; (4) necrotic teeth; (5) occurrence of sealer extrusion; (6) single visit; (7) multiple visits; (8) primary endodontic treatment; (9) endodontic retreatment; (10) anterior teeth; and (11) posterior teeth.

Assessment of certainty of evidence

The certainty of evidence of the included studies was assessed using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) tool (GRADEpro GDT: GRADEpro Guideline Development Tool [Software]. McMaster University, 2015 (developed by Evidence Prime Inc.)[18]. The GRADE tool has five domains that can be downgraded and reduce the certainty of the evidence (Grades of Recommendation Assessment Development & Evaluation (GRADE) Working Group 2004), as follows:

1. Risk of bias;
2. Inconsistency;
3. Indirectness;
4. Imprecision;
5. Other consideration.

RESULTS

Study selection

Figure 1 presents the flow diagram for the search strategy. Initial screening of databases resulted in 631 studies, with 91 being duplicates. After reading and analyzing the titles and abstracts, 530 articles were excluded. Ten studies[19-28] were accessed for full-text reading. One study[19] was excluded for not having evaluated bioceramic sealers. One study[29] was retrieved from the reference list of the included studies. Finally, ten studies[20-29] were included in the present review.

Data extraction

Table 2 shows the characteristics of the included studies.

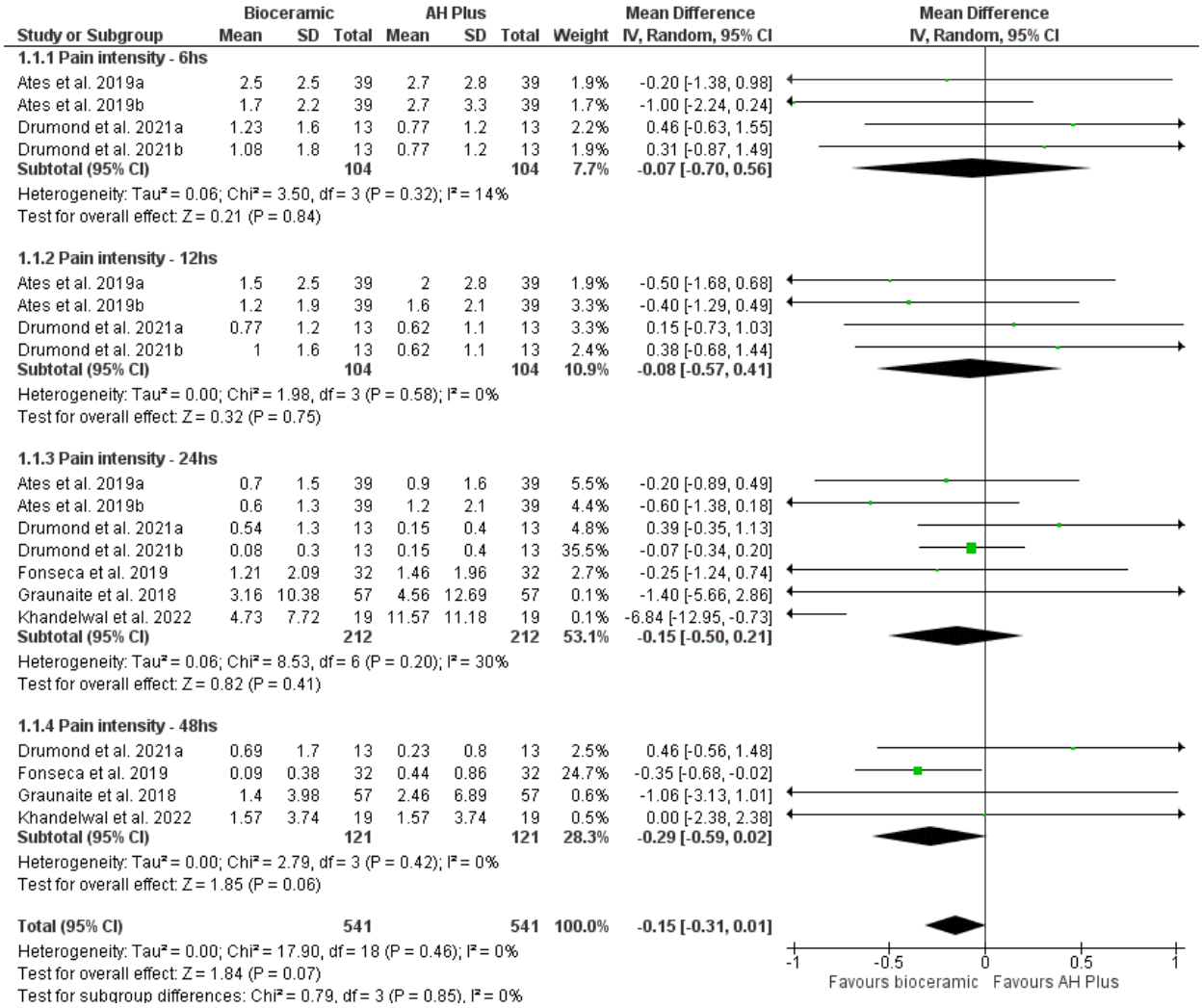


Figure 3. Forest plot of the postoperative pain intensity between bioceramic sealers and AH Plus at 6-, 12-, 24-, and 48hs.

Footnote: Ates et al. 2019a – results on vital teeth; Ates et al. 2019b – results on necrotic teeth; Drumond et al. 2021a – results on Endosequence BC sealer; Drumond et al. 2021b – results on Bio-C sealer.

Additional information on mean and standard deviation values of postoperative pain was obtained from the authors of one study[22]. No other information was obtained.

The bioceramic sealers evaluated were Endosequence BC[22,24], Endoseal MTA[22,25], iRoot SP[21], Bio-C Sealer[24], Sealer Plus BC[20], Total-Fill BC[23,26], BioRoot RCS[27,29], Endoseal TCS[28]. All studies tested AH Plus sealer as the comparison group. Additionally, one study evaluated Tubli-Seal[27].

The evaluated teeth differ among studies. Fonseca *et al.*[20] analyzed maxillary anterior teeth; Tan *et al.*[26] evaluated anterior and posterior teeth; Graunaite *et al.*[23] investigated maxillary and mandibular anterior teeth and premolars; Khandelwal *et al.*[27] included only maxillary anterior teeth; Kim *et al.*[28], Shim *et al.*[25] and Paz *et al.*[29] included all types of teeth; Ates *et al.*[21] selected mandibular premolars and molars; Drumond *et al.*[24] included only molars with three root canals; and Aslan *et al.*[22] included mandibular first and second molars. Teeth diagnoses also varied among studies. Four studies included symptomatic and asymptomatic vital and necrotic teeth[21,25,26,28]. One study included teeth presenting symptomatic chronic apical periodontitis[27].

One study only included asymptomatic necrotic teeth[20]. One study included asymptomatic irreversible pulpitis and asymptomatic necrotic teeth[29]. One study included only teeth presenting asymptomatic apical periodontitis[23]. And two studies included only teeth presenting asymptomatic irreversible pulpitis[22,24].

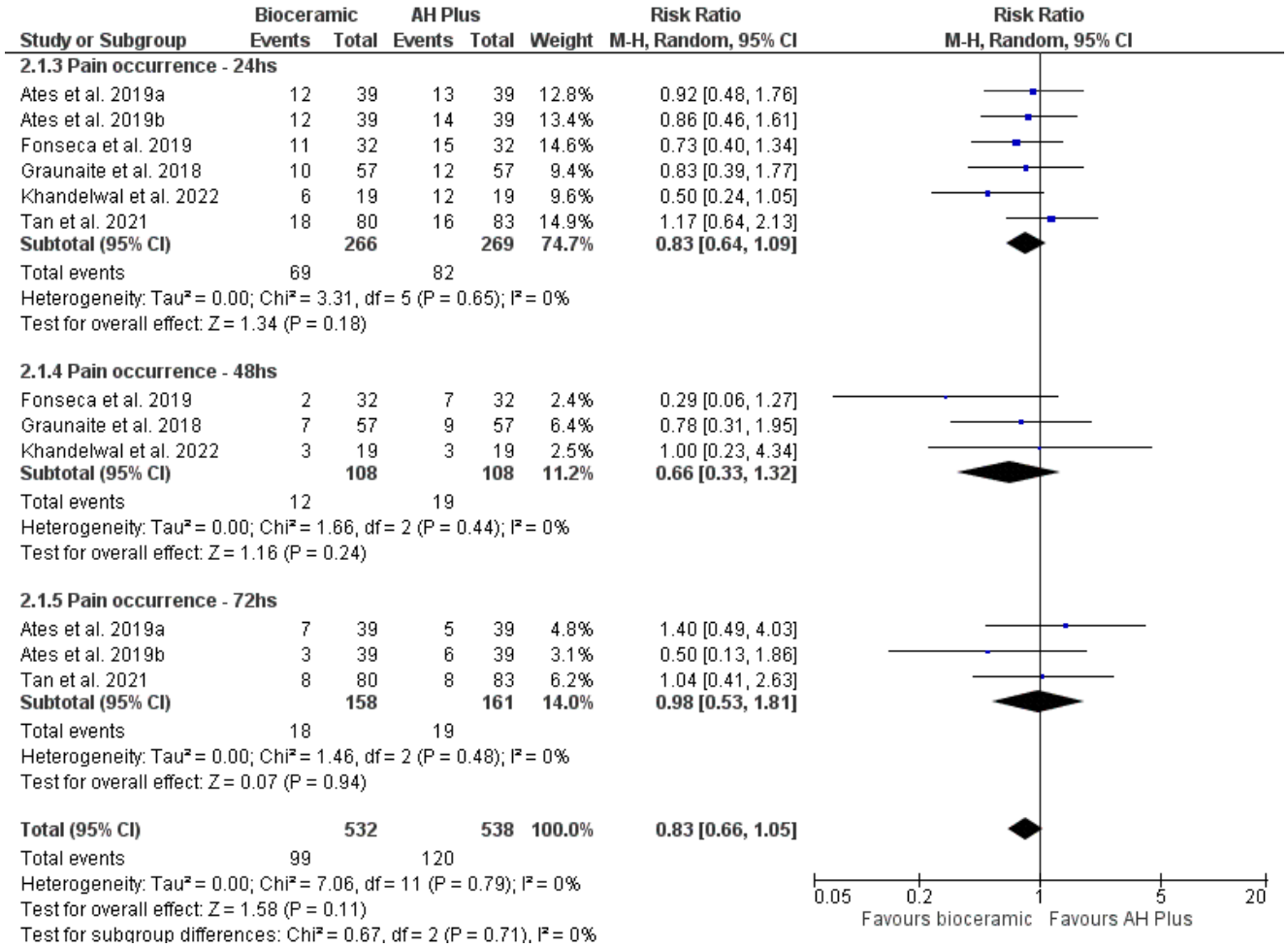


Figure 4. Forest plot of the postoperative pain incidence between bioceramic sealers and AH Plus at 24-, 48- and 72hs.

Footnote: Ates et al. 2019a – results on vital teeth; Ates et al. 2019b – results on necrotic teeth.

The majority of the studies performed single visit root canal treatments[20-22,24,25]. One study performed single visit root canal retreatment[23]; two studies performed single- and multiple-visits root canal treatment or retreatment[26,29]; one study performed multiple-visit root canal treatment[27]; and one multiple-visit root canal treatment and retreatment[28].

As for the obturation technique, two studies used only the single cone technique[20,22]; one study performed the single cone and warm vertical condensation technique[24]; one used only the warm vertical condensation technique[23]; one tested only the carrier-based obturation technique[21]; one study performed the lateral condensation technique[27]; and four studies used different obturation techniques for the bioceramic and AH Plus groups[25,26,28,29].

All studies assessed filling quality through radiographic images, except for Paz *et al.*[29] and Aslan *et al.*[22], which did not describe how this was performed. In relation to the pharmacological prescription for pain control, five studies reported for prescription of ibuprofen[20-22,26,29]; only one study reported for prescription of paracetamol or tramadol, in case of ibuprofen allergy[26]. Additionally, five studies did not inform for methods of pharmacological pain control[23-25,27,28].

Regarding the assessment of postoperative pain intensity, three studies employed Visual Analogue Scale (VAS), measuring pain in a score of 0-10cm[20,21,29]. In addition, four studies measured pain levels with VAS from 0-100mm[22,23,25,27]. One study employed a visual scale ranging from 0-10cm[24]; one study employed a numerical rating scale ranging from 0-10[28]; and one study used the 5-point Likert scale[26].

In relation to the main findings, only one study reported lower postoperative pain for the bioceramic sealer (BioRoot RCS) when

compared to AH Plus and Tubli-Seal[27]. None of the other included studies found any differences on the postoperative pain intensity among the evaluated sealers[20-26,28,29].

Endodontic sealer extrusion and its influence on postoperative pain was evaluated by five studies[20,21,24,26,27]. Of these, one study reported a greater extrusion for the bioceramic sealer[20], and one study a greater extrusion for the AH Plus[26].

Additionally, three studies reported that the type of teeth, being premolars and molars, were associated to greater incidence and intensity of postoperative pain[21,23,29]; and one described that premolar tooth treated with AH Plus were more associated to greater pain intensity than those treated with the bioceramic sealer[21].

Finally, five studies evaluated the need for medication intake[20,21,22,23,26]. Four studies reported no differences among groups[20,22,23,26]; one study reported a higher need for medication intake for AH Plus at 0-12hs in treatments performed in vital teeth[21]. Additionally, one study reported that medication intake was associated with a VAS score higher than 30mm[23].

Assessment of Risk of Bias

Figure 2 summarizes the risk of bias of the randomized clinical trials.

Of the ten randomized controlled trials included, eight were classified as a low-risk bias[20-27]; and two were classified as some concerns risk of bias[28,29].

Meta-analysis

Only studies presenting data as mean and standard deviation were included in meta-analysis of continuous data. Therefore, four studies were excluded[22,25,28,29]. In addition, meta-analysis of data presenting zero values were not considered, since this can generate computational problems[16]. Thus, meta-analyses for pain intensity and pain incidence (number of events) after 72hs and need for medication intake after 48 and 72hs were not performed. Meta-analysis for postoperative pain intensity (mean ± standard deviation) after 6, 12, 24 and 48 hours[20,21,23,24,27] was performed. The study from Tan *et al.*[26] was excluded since pain was quantified by using a 5-point Likert scale, while other studies used VAS scale. The study from Ates *et al.*[21] was considered twice since data for this outcome was displayed stratified (necrotic and vital teeth).

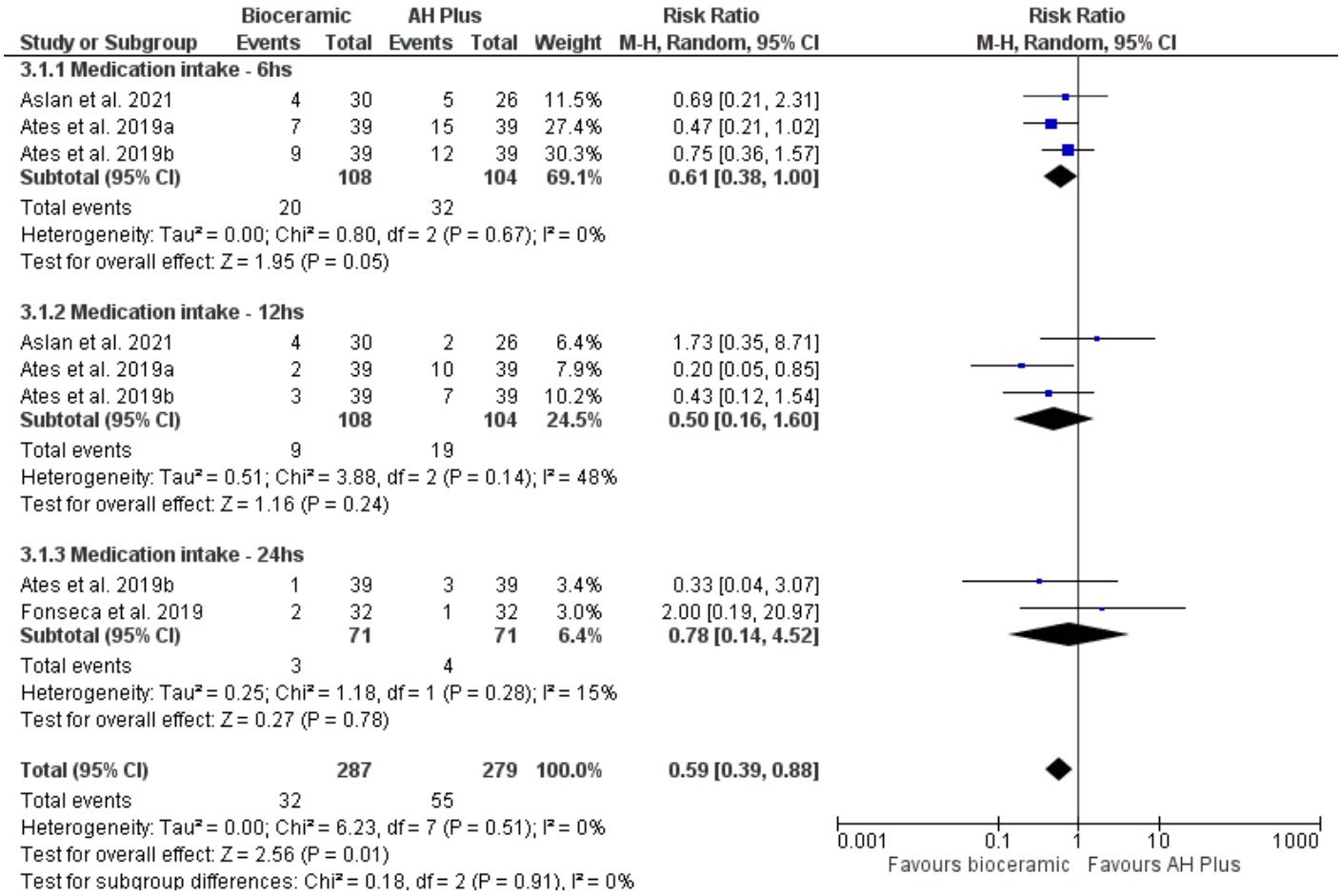


Figure 5. Forest plot of the number of medication intake between bioceramic sealers and AH Plus at 6-, 12- and 24hs.
Footnote: Ates et al. 2019a – results on vital teeth; Ates et al. 2019b – results on necrotic teeth.

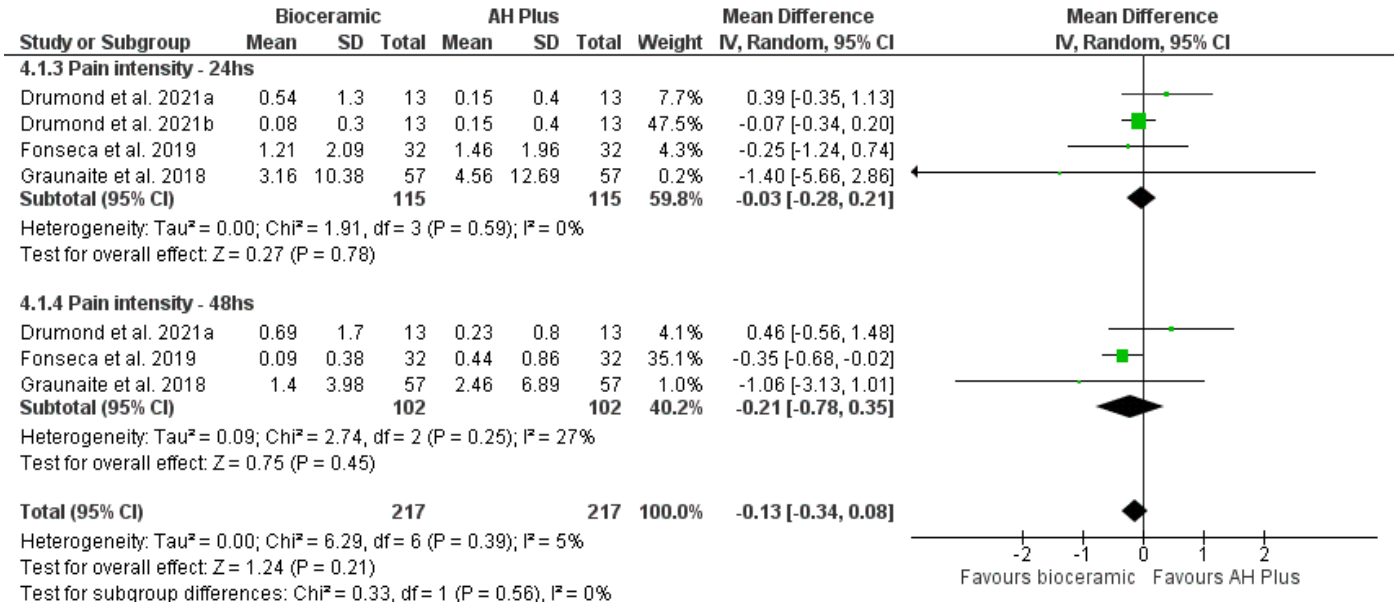


Figure 6. Sensitivity analysis considering only data on asymptomatic and necrotic teeth.
Footnote: Drumond et al. 2021a – results on Endosequence BC sealer; Drumond et al. 2021b – results on Bio-C sealer.

Additionally, the study from Drumond *et al.*[24] also was considered twice since data was stratified according to both bioceramic sealers used (Endosequence BC Sealer and Bio-C Sealer).Since this outcome was provided as continuous variables, the effect measure was the mean difference, and the statistical method was the inverse variance DerSimonian-Laird test. No significant differences were verified for the overall effect [P = 0.07; MD = -0.15 (-0.31, -0.01); I^2 = 0%]. Subgroup analysis showed no differences in all times evaluated, as illustrated in **Figure 3**.

For the total number of events of postoperative pain, a meta-analysis was feasible for events after 24, 48 and 72 hours [20,21,23,26,27]. As this is a dichotomous variable, the Mantel-Haenszel test was applied, and a risk ratio was considered. No significant differences were verified for the overall effect [P = 0.11; RR = 0.83 (0.66, 1.05); I^2 = 0%] and for subgroup analysis, regardless the assessed time, as presented in **Figure 4**.

For the total number of analgesic intakes, a meta-analysis was feasible for 6, 12 and 24 hours[20-22]. As this is a dichotomous variable, the Mantel-Haenszel test was applied, and a risk ratio was considered. Significant differences were observed on the overall effect [P = 0.01; RR = 0.59 (0.39, 0.88); I^2 = 0%], favoring a less consumption of medications for the bioceramic sealers. Significant differences were also for subgroup analysis after 6hs [P = 0.05; RR = 0.61 (0.38, 1.00); I^2 = 0%] as shown in **Figure 5**.

Since less than ten studies were included in each individual meta-analysis, no funnel plot was generated for detecting publication bias.

Sensitivity analysis

Sensitivity analysis for vital teeth was not feasible since only one study stratified data for vital and necrotic teeth[21]. Sensitivity analysis for multiple visits was not possible because only one study from those included in meta-analyses performed multiple-visit root canal treatments[27]; and another study performed multiple visits root canal retreatments[23]. Finally, sensitivity analysis for anterior and posterior teeth, symptomatic vital and necrotic teeth, and asymptomatic vital teeth were not possible since no study presented data based on tooth position., or stratified data for symptomatic/asymptomatic vital and symptomatic necrotic teeth.

For all sensitivity analysis performed, the effect measure was the mean difference, a random effect model was adopted, and the statistical method was the inverse variance DerSimonian-Laird test, since all data were continuous data.

In the sensitivity analysis considering only studies that investigated pain intensity in asymptomatic necrotic teeth, three studies were included based on their available data[20,23,24].

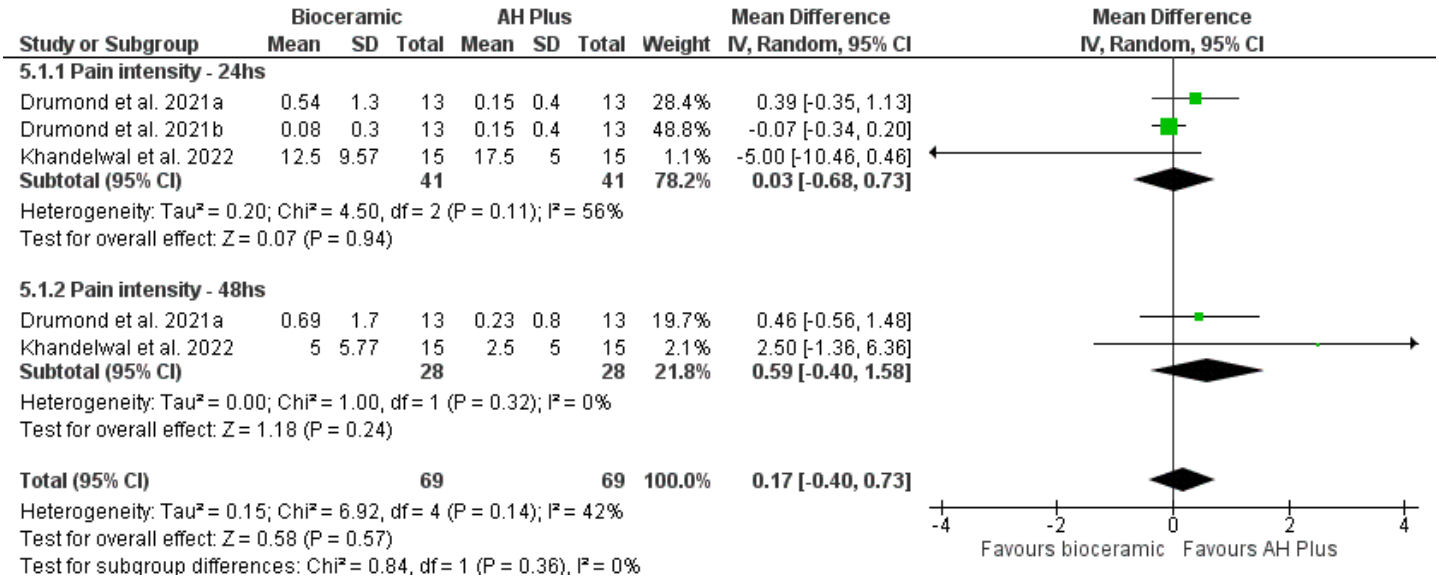


Figure 7. Sensitivity analysis considering only data on presence of sealer extrusion.
Footnote: Drumond et al. 2021a – results on Endosequence BC sealer; Drumond et al. 2021b – results on Bio-C sealer.

Meta-analyses were performed for 24 and 48hs. No significant differences were verified for the overall effect [P = 0.21; MD = -0.15 (-0.13, 0.08); I^2 = 5%] and for subgroup analysis, regardless the assessed time, as presented in **Figure 6.**

In the sensitivity analysis considering studies that presented data for the occurrence of sealer extrusion and pain intensity, two studies were included based on their available data[24,27]. Despite Fonseca *et al.*[20] had evaluated sealer extrusion, they did not stratified data on the occurrence of extrusion or not. Therefore, it was not possible to include this study in the present analysis. Meta-analyses were performed for 24 and 48hs. No significant differences were verified for the overall effect [P = 0.57; MD = 0.17 (-0.40, 0.73); I^2 = 42%] and for subgroup analysis, as shown in **Figure 7**.

As for the sensitivity analysis considering studies that presented data when sealer extrusion did not occur, two studies were included based on their available data[23,27]. Meta-analyses were also performed for 24 and 48hs, and no significant differences were verified for the overall effect [P = 0.18; MD = -1.16 (-2.85, 0.53); I^2 = 0%] and for subgroup analysis, as illustrated in **Figure 8**.

A sensitivity analysis was performed considering only studies that performed single visit primary root canal treatments. Two studies were included based on their available data[20,24]. Meta-analyses were also performed for 24 and 48hs and, once again, no significant differences were verified for the overall effect [P = 0.42; MD = -0.10 (-0.35, 0.15); I^2 = 23%] and for subgroup analysis, as depicted in **Figure 9**.

Finally, a sensitivity analysis was performed for number of medication intake, excluding data of vital teeth from the study of Ates *et al.*[21], as presented in Figure 10. Meta-analyses were performed for 6, 12 and 24hs. No significant differences were observed for the overall effect [P = 0.24; RR = 0.74 (0.44, 1.23); I^2 = 0%] and for subgroup analysis.

Certainty of evidence

GRADE results are displayed in **Table 3**. The GRADE tool demonstrated a low certainty of evidence for all analyses. The overall certainty of evidence was assessed for postoperative pain intensity at 6, 12, 24, and 48hs; for pain incidence at 24hs, 48hs and 72hs; and for risk of medication intake at 6, 12 and 24hs. For all analyses, the studies received the "not serious" classification for risk of bias, inconsistency, and indirectness; and the "very serious" classification for imprecision. "Other considerations" domain did not influence the certainty of evidence.

DISCUSSION

Even though endodontic sealers should be retained inside the root canal, they can present some degree of influence in inflammatory responses of the periapical tissues, especially when accidentally extruded beyond the root canal foramen[31]. Therefore, although bioceramic sealers present greater biological properties when compared to other endodontic sealers, it is necessary to evaluate their influence in postoperative pain incidence and intensity compared to other available sealers.

This systematic review aimed to compare the incidence and intensity of postoperative pain when bioceramic sealers were used and compared to other sealers, without limiting to one specific sealer. However, all studies used AH Plus as the comparison group, since this is, up to this moment, the gold standard sealer, and only one study also compared to a zinc oxide-eugenol sealer. Even though systematic reviews comparing the postoperative pain incidence and intensity of bioceramic sealers already exists[32-35], a few drawbacks were verified. One had considered a salicylate resin-based sealer containing mineral trioxide aggregate as a bioceramic-sealer[32], and another had considered a reparative material as an endodontic sealer[35]. These criteria could hamper the results since it does not reflect the results for bioceramic sealers. Furthermore, unlike two previous reviews[33,34], in the present review several sensitive analyzes were conducted in order to verify isolated effects on the intensity of postoperative pain. And finally, since the publishing of these previous systematic reviews, few studies on the subject were published[24,25,27,28], making it necessary the performance of the present review. In the present systematic review, meta-analyses were performed for postoperative pain intensity, incidence (number of events) and number of medication intake. Regarding the results of postoperative pain intensity, meta-analyses indicated no differences among bioceramic and epoxy resin-based sealers in any of the evaluated periods. Sensitivity analyses were performed for asymptomatic necrotic teeth, teeth with and without sealer extrusion, and treatments performed in single visit. Sensitivity analyses were performed for asymptomatic necrotic teeth, teeth with and without sealer extrusion, and treatments performed in single visit. Once again, no differences were observed. Additionally, studies that were not included in meta-analyses also concluded that there were no differences in the postoperative pain intensity between bioceramic and epoxy-resin based sealers[22,25,28,29]. In relation to the incidence of postoperative pain, meta-analyses also indicated no differences among bioceramic and epoxy resin-based sealers in any of the evaluated periods. Therefore, based on these results, it is possible to suggest that there are no differences in the postoperative intensity between bioceramic and epoxy resin-based sealers.

Controversially, results from meta-analyses of number of medication intake demonstrated a significant difference, indicating a lower need for medication intake for the bioceramic group at 6hs postoperatively. However, when sensitivity analysis was performed, excluding data from vital teeth, no differences were observed in any assessed period of time. This result probable indicate that the significant difference verified in the general meta-analyses for number of medication intake is probably related to the preoperative diagnosis of symptomatic vital teeth. Preoperative pain can influence in the occurrence of postoperative pain, and this can probably explain the above-mentioned results, as previously reported[36].

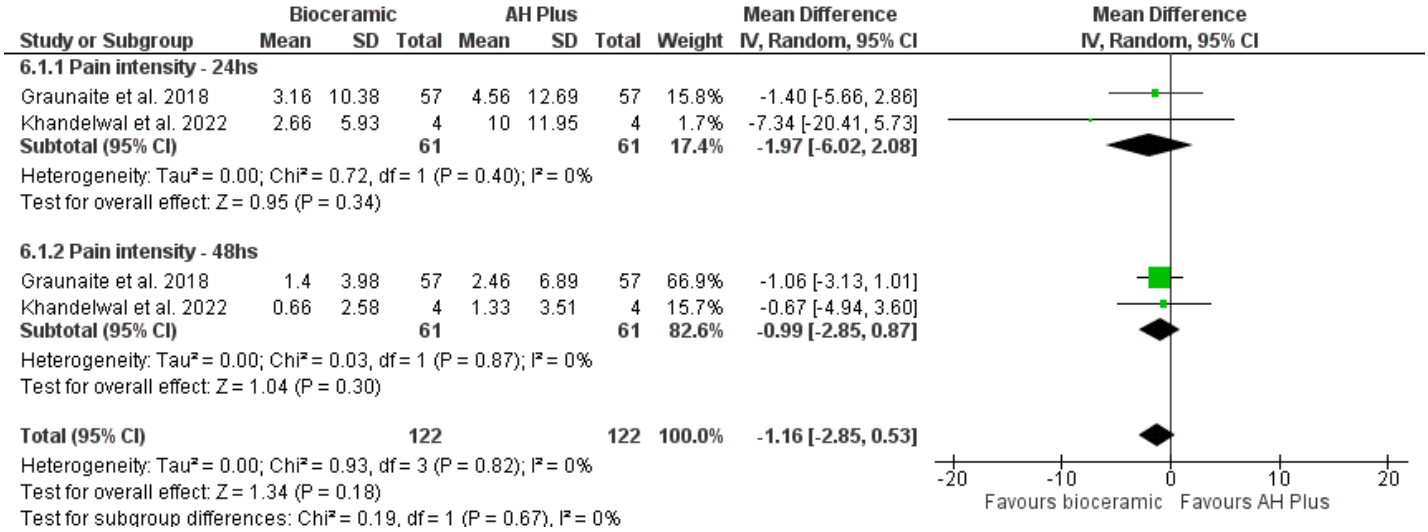


Figure 8. Sensitivity analysis considering only data on absence of sealer extrusion.

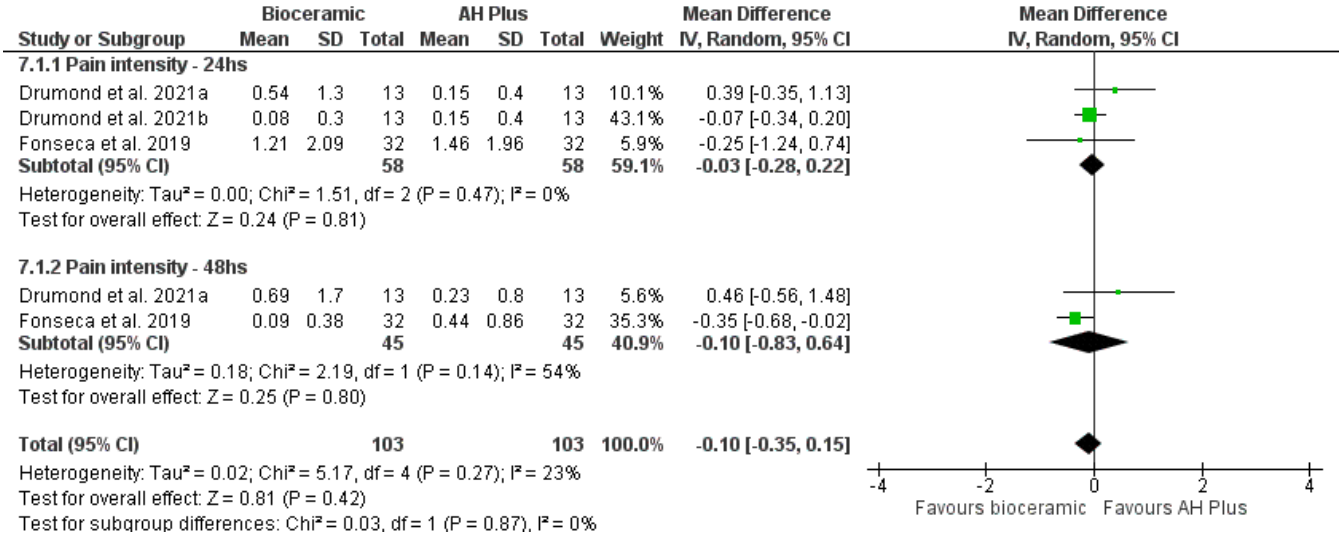


Figure 9. Sensitivity analysis considering only data on sigle visit root canal treatment.
Footnote: Drumond et al. 2021a – results on Endosequence BC sealer; Drumond et al. 2021b – results on Bio-C sealer.

Nevertheless, three studies reported an increased postoperative pain for posterior teeth[21,23,29]. It has been previously reported that an increased postoperative pain incidence is related to treatments performed in molars and premolars, mainly due to their difficult anatomies which could increase the chance of procedural errors that could result in increased postoperative pain[37]. Therefore, these results cannot be directly related to the sealers since other factors, such as debris or bacteria extrusion, could present direct effects on postoperative pain incidence/intensity[38,39].

Only one study compared the results of postoperative pain of a bioceramic sealer to a zinc oxide-eugenol sealer, additionally to AH Plus[27]. According to their results, the zinc oxide-eugenol sealer influenced higher pain scores compared to the bioceramic and epoxy resin sealer, even after 72hs. This result is in agreement with a previous study in which demonstrated that zinc oxide-eugenol sealers are highly cytotoxic and have the potential to exacerbate the inflammatory process, mostly due to the presence of eugenol[40].

Despite presenting some degree of cytotoxicity, bioceramic sealers can favor the healing process of periapical tissues, reducing inflammation, and inducing odontoblast differentiation and mineralization into pre-osteoblasts[41]. This sealer has already demonstrated a lower cytotoxic effect when compared to AH Plus *in vitro*[42-44]. Surprisingly, the included studies reported that sealer extrusion was not associated with an increased postoperative pain. This fact could indicate that a small number of sealers extruding to periapical tissues does not necessarily reflect on an increased postoperative pain intensity. However, not increasing postoperative pain intensity does not mean that inflammatory reactions on the periapical tissues do not occur[8].

Risk of bias assessment showed that from the ten included studies, eight had an overall low risk of bias[20-27], and two had an overall some concerns risk of bias[28,29]. This was mainly due to the lack of information regarding the randomization process[29], and due to the not availability of outcomes for several participants[28].

As for the overall certainty of evidence, the GRADE tool demonstrated a low certainty of evidence for all analyses. Subgroup analyses for postoperative pain incidence and intensity were considered since they provide different information according to the periods analyzed. In the domain 'risk of bias', a 'not serious' classification was ascribed since none of the included studies presented a high risk of bias, and the majority of the studies had a low risk of bias[45]. In the domain 'inconsistency', a 'not serious' classification was attributed since no substantial heterogeneity was verified among the included studies, as presented in the meta-analysis results[46]. In the domain 'indirectness', a 'not serious' classification was attributed since no included studies performed indirect comparisons or presented indirect results[47]. In the domain 'imprecision', a 'very serious' classification was assigned because optimal information size (pooled sample size of 300) was not met, and confidence intervals were under 0.75 or above 1.25[48].

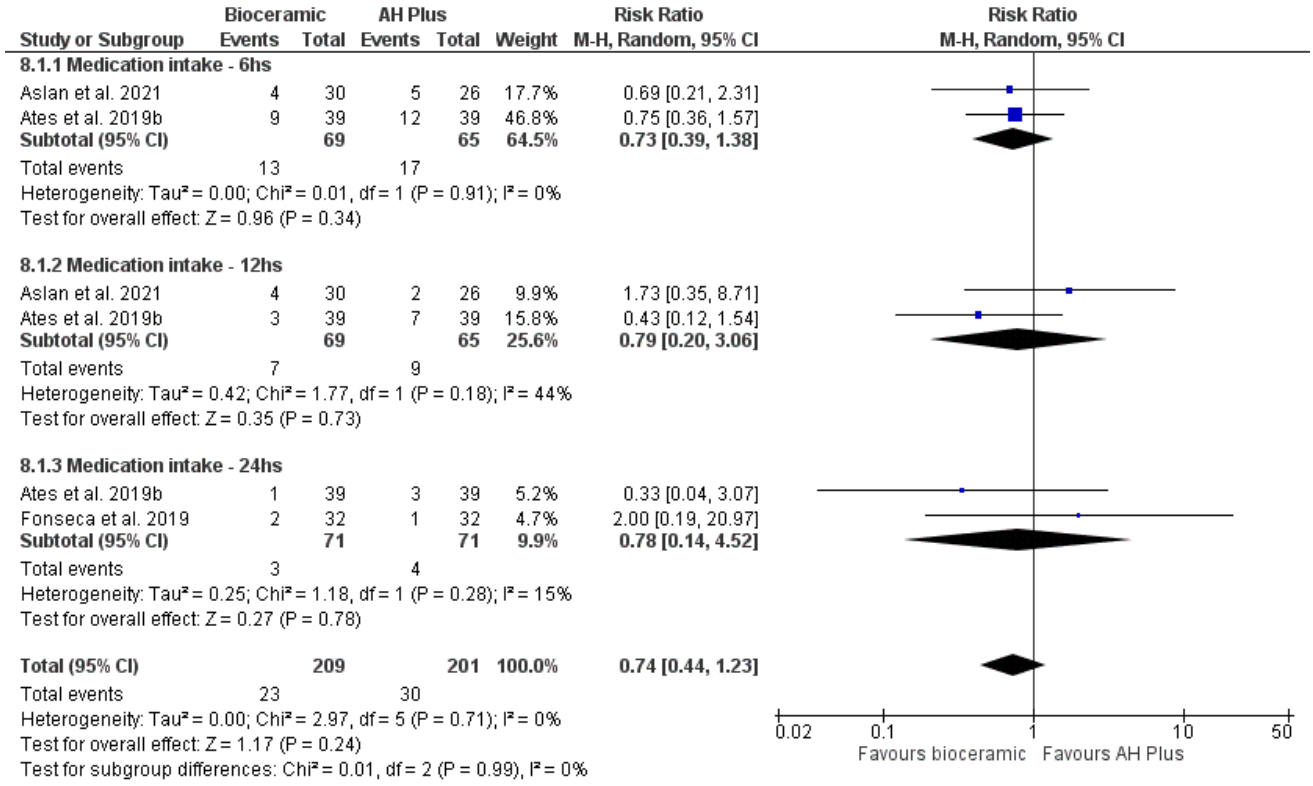


Figure 10. Sensitivity analysis of number of medication intake excluding results of vital teeth from Ates et al. 2019.

Regarding the domain 'other considerations', none of the domains' criteria (publication bias, large effect, plausible confounding and dose-response gradient) were observed in the included studies[49].

The strength of this systematic review is related to the systematic approach in data collection, based on an *a priori* registered protocol. Only randomized clinical trials were included and cautiously analyzed in order to provide solid evidence about the investigated topic. However, this systematic review presents some limitations. Based on the information provided by the included studies, it was not possible to stratify the data based on the symptomatic and asymptomatic vital teeth, and symptomatic necrotic teeth, which can significantly impact the investigated outcome. Sensitivity analysis on tooth position was also not possible, despite the results presented by some studies. Finally, procedural factors such as debris/bacteria extrusion, irrigant extrusion and instrument aggression to the periapical tissues were also not possible to be determined, not allowing further discussion on the influence of such aspects on the provided results.

Therefore, within the limitations of the present review, it may be pointed out that there are no differences in the postoperative pain intensity and incidence following obturation with bioceramic sealers and AH Plus. Differences on number of medication intake may be related to the preoperative diagnosis. Additionally, zinc oxide-eugenol sealers seem to cause more intense postoperative pain when compared to bioceramic sealers and AH Plus. Nevertheless, this assumption is based on a low certainty of evidence, making further studies necessary.

CONCLUSION

With a low certainty of evidence, there seem to be no differences between bioceramic sealers and AH Plus regarding postoperative pain intensity and incidence. Number of medication intake seem to be associated to the preoperative diagnosis. Zinc oxide-eugenol evoked a more pronounced postoperative pain. Well-designed studies are needed to increase the certainty of evidence.

Table 2. Characteristics of the included studies.

Author(s) (Year of publication) - Country	Sealers evaluated	Participant's age (mean ± SD per group)	Number of treated teeth (per group)	Teeth included	Teeth diagnosis	Treatment performed	Obturation technique	Methods of obturation quality assessment	Pharmacological prescription for pain control	Methods of postoperative pain assessment	Intervals of pain assessment	Outcomes	Main findings
Aslan et al. (2021) - Turkey	Endoseal MTA; Endosequence BC; AH Plus	18 – 60 years (Endoseal MTA: 39.57±13.09; Endosequence BC: 32.46±13.20; AH Plus: 37.15±11.93)	n = 90 (Endoseal MTA group = 30; EndoSequence BC group = 30; AH Plus group = 30)	Mandibular first and second molar	Asymptomatic irreversible pulpitis	Single visit root canal treatment	Single cone technique	NR	Ibuprofen 400 mg	Visual Analogue Scale (VAS) ranging from 0 – 100mm; A form to report the frequency of drug intake	6, 12, 24, 48h, 3rd, 4th, 5th, 6th and 7th days after treatment	No differences among groups at any times; No differences observed analgesic intake among groups; Pain and analgesic intake significantly decreased after 12 hours; No reports of postoperative pain after 24hs	Tested sealers had similar levels of postoperative pain and analgesic intake
Ates et al. (2019) - Turkey	iRoot SP (ISP); AH Plus	18 – 65 years (AH Plus–V – Vital teeth: 30.69±10.39; AH Plus-D – Devital teeth: 36.33±11.08; ISP-V – Vital teeth: 35.00±12.55; ISP-D – Devital teeth: 40.69±11.87)	n = 160 (AH Plus–V = 40; AH Plus-D = 40; ISP–V = 40; ISP–D = 40)	Mandibular premolars and molars	Symptomatic and asymptomatic vital and necrotic teeth	Single visit root canal treatment	Carrier-based obturator technique	Radiographically	Ibuprofen 200mg	10cm visual analogue scale (VAS) Manual record of number and timing (by hour) of analgesic intake	Preoperatively: before local anesthesia; Postoperatively: 6, 12, 24, and 72h	No differences among groups at any times; Higher analgesic intake for patients with vital teeth treated with AH Plus compared to the other groups at 0–6 and 6–12 h, and for molars treated with AH Plus at 6-12hs; Premolars treated with iRoot SP had significantly less pain intensity than premolars treated with AH Plus; There was no correlation between sealer extrusion and pain intensity or analgesic intake	Tested sealers did not significantly affect pain levels; iRoot SP was associated with less analgesic intake compared to AH Plus sealer

Drumond et al. (2021) - Brazil	Endosequence BC Sealer; Bio-C Sealer; AH Plus	18 – 60 years	n = 39 (Endosequence BC Sealer = 13; Bio-C Sealer = 13; AH Plus = 13)	Molars with 3 independents root canals	Asymptomatic irreversible pulpitis	Single visit root canal treatment	Single cone technique Warm vertical condensation technique	Radiographically	NR	Visual scale ranging from 0 – 10cm	12, 24, 48h and 7 days	No differences among groups at any times; AH Plus and Bio-C Sealer had a significant reduction in pain after 12h; Endosequence BC did not differ in pain intensity, even after 7 days, without differences; There was no difference in the incidence of extrusion among groups	Postoperative pain results among groups were similar and with low intensity
Fonseca et al. (2019) - Brazil	Sealer Plus BC; AH Plus	15 – 68 years (Sealer Plus BC: 38.5±14.18; AH Plus: 37.09±13.10)	n = 64 (Sealer Plus BC = 32; AH Plus = 32)	Single-rooted, maxillary anterior teeth with straight canals	Asymptomatic, pulp necrosis	Single visit root canal treatment	ingle cone echnique	Radiographically	600 mg Ibuprofen, every 6 hours if experience pain	VAS ranging from 0 – 10cm; Manual record of number of tablets taken for pain relief	24, 48, 72h and 7 days	There was no report of pain after 48 hours; There was no report of flare-up at any time-point; No differences among groups at any times regarding pain level and medication intake; Sealer Plus BC presented a significant higher extrusion than AH Plus; without correlation on pain occurrence	No differences were observed among sealers regarding pain intensity and medication intake; Sealer Plus BC showed more extrusion, without association with pain occurrence
Graunaite et al. (2018) - Lithuania	TotalFill BC; AH Plus	NR	n = 122 (TotalFill BC = 61; AH Plus = 61)	Maxillary and mandibular anterior teeth and premolars	Asymptomatic apical periodontitis	Single visit root canal retreatment	Warm vertical condensation technique	Radiographically	NR	VAS ranging from 0 – 100mm; Manual record of medication intake	24, 48, 72h and 7 days	No differences among groups at any times; No pain was reported after 72h; Intake of medication was associated with a VAS score higher than 30mm; Pain occurrence was higher in mandibular premolars	Occurrence and intensity of postoperative pain was similar for both sealers

Khandelwal et al. (2022) - India	Tubli-Seal; BioRoot RCS AH Plus	18-60 years (Tubli-Seal: 41.57; BioRoot RCS: 43.63 AH Plus: 41.68)	n = 63 (Tubli-Seal = 21; BioRoot RCS = 21; AH Plus = 21)	Maxillary anterior teeth	Symptomatic, chronic apical periodontitis	Multiple-visit root canal treatment	Lateral condensation technique	Radiographically	NR	VAS ranging from 0 – 100mm; Manual record of type and number of medications taken	24, 48, 72h and 7 days	No differences among groups at any times, except for Tubli-Seal and BioRoot RCS at 24h; Regarding sealer extrusion, none of the sealers showed significant differences; At 72h, pain scores were reported only for Tubli-Seal group; At 7 days, there were no pain reports	Postoperative for BioRoot RCS was lower compared to AH Plus and Tubli-Seal
Kim et al. (2022) – South Korea	Endoseal TCS AH Plus	> 18 years	n = 74 (Endoseal TCS = 35; AH Plus = 39)	Anterior and posterior teeth	Symptomatic and asymptomatic vital and necrotic teeth	Multiple-visit root canal treatment or retreatment	Endoseal TCS: sealer-based obturation; AH Plus: continuous wave of condensation	Radiographically	NR	Numeric Rating Scale (NRS) –0-10	4, 24 and 48h	There were no differences in postoperative pain between groups;	Both sealers had similar results on postoperative pain scores
Paz et al. (2018) - Portugal	BioRoot RCS; AH Plus	NR	n = 30 (BioRoot RCS = 10; AH Plus-1 = 10; AH Plus-2 = 10)	Anterior and posterior teeth	Asymptomatic irreversible pulpitis and pulp necrosis	One- or multiple - visit root canal treatment or retreatment	BioRoot RCS group: single cone technique; AH Plus groups: lateral condensation (AH Plus-1) or continuous wave of condensation (AH Plus-2)	NR	Ibuprofen 600 mg	VAS ranging from 0 – 10cm;	24, 48, 72, 96, 120, 144 and 168h	BioRoot RCS + single had higher postoperative pain incidence, Regarding pain intensity, there were no differences among groups at any times; Post-operative pain was more frequent and intense in posterior teeth	BioRoot RCS had higher reports of postoperative pain, but without differences on pain intensity Posterior teeth were more associated to postoperative pain
Shim et al. (2021) – South Korea	Endoseal MTA; AH Plus	19 – 70 years	n = 67 Group A (AH Plus = 15; Endoseal MTA = 17) Group B (AH Plus = 17; Endoseal MTA = 18)	Anterior Teeth (Groups A); Premolars and molars (Groups B)	Symptomatic and asymptomatic vital and necrotic teeth	Single visit root canal treatment	Endoseal MTA group: single cone technique AH Plus group: continuous wave technique	Radiographically	NR	VAS ranging from 0 – 100mm;	1, 2, 3, 4, 5, 6 and 7 days	No differences among sealers on postoperative pain intensity or incidence, regardless of the type of teeth	Endoseal MTA and AH Plus had similar results on incidence and intensity of postoperative pain

Tan et al. (2021) - Singapore	TotalFill BC; AH Plus	> 21 years	n = 171 (TotalFill BC = 84; AH Plus = 87)	Anterior teeth, premolars and molars	Symptomatic and asymptomatic vital and necrotic teeth	One- or multiple - visits root canal treatment or retreatment	TotalFill BC group: TotalFill BC point; AH Plus group: non-standardized gutta-percha cones; Additional accessory cones were used if the canal was broad or irregularly shaped	Radiographically	Ibuprofen; If allergic, paracetamol or tramadol	Pain diary recorded as “no pain” (score=0) or a 5-point Likert; Manual record of dose and frequency of medication intake	1, 3 and 7 days	AH Plus was associated to more extrusion; without influence on postoperative pain experience; No differences among groups at any times; There were no differences regarding medication intake	Tested sealers did not differ regarding postoperative pain

Table 3. Overall certainty of the evidence from the included studies.

Certainty assessment						Effect		Certainty
Nº of studies – Study design	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Relative (95% CI)**	**Absolute (95% CI)**	
Pain intensity – 6h								
2 randomized trials	Not serious	Not serious	Not serious	Very serious [a]	None	-	MD 0.07 lower (0.7 lower to 0.56 higher)	⊕⊕◯◯ Low
Pain intensity - 12h								
2 randomized trials	Not serious	Not serious	Not serious	Very serious [a]	None	-	MD 0.08 lower (0.57 lower to 0.41 higher)	⊕⊕◯◯ Low
Pain intensity - 24h								
5 randomized trials	Not serious	Not serious	Not serious	Very serious [a]	None	-	MD 0.15 lower (0.5 lower to 0.21 higher)	⊕⊕◯◯ Low
Pain intensity - 48h								
4 randomized trials	Not serious	Not serious	Not serious	Very serious [a]	None	-	MD 0.29 lower (0.59 lower to 0.02 higher)	⊕⊕◯◯ Low
Pain incidence- 24h								
5 randomized trials	Not serious	Not serious	Not serious	Very serious [a]	None	RR 0.83 (0.64 to 1.09)	52 fewer per 1.000 (from 110 fewer to 27 more)	⊕⊕◯◯ Low
Pain incidence - 48h								
3 randomized trials	Not serious	Not serious	Not serious	Very serious [a]	None	RR 0.66 (0.33 to 1.32)	60 fewer per 1.000 (from 118 fewer to 56 more)	⊕⊕◯◯ Low
Pain incidence - 72h								
2 randomized trials	Not serious	Not serious	Not serious	Very serious [a]	None	RR 0.83 (0.53 to 1.81)	20 fewer per 1.000 (from 55 fewer to 96 more)	⊕⊕◯◯ Low
Medication intake - 06h								
2 randomized trials	Not serious	Not serious	Not serious	Very serious [a]	None	RR 0.61 (0.38 to 1.00)	120 fewer per 1.000 (from 191 fewer to 0 fewer)	⊕⊕◯◯ Low
Medication intake – 12h								
2 randomized trials	Not serious	Not serious	Not serious	Very serious [a]	None	RR 0.50 (0.16 to 1.60)	91 fewer per 1.000 (from 153 fewer to 110 more)	⊕⊕◯◯ Low
Medication intake - 24h								
2 randomized trials	Not serious	Not serious	Not serious	Very serious [a]	None	RR 0.78 (0.14 to 4.52)	12 fewer per 1.000 (from 48 fewer to 198 more)	⊕⊕◯◯ Low

REFERENCES

1. Sipavičiūtė E, Manelienė R. Pain and flare-up after endodontic treatment procedures. Stomatologija. 2014;16(1):25-30.

2. Mathew ST. Post operative pain in endodontics: A systemic review. Journal of Dentistry and Oral Hygiene. 2015;7(8):130-7.

3. Raja SN, Carr DB, Cohen M, Finnerup NB, Flor H, Gibson S, et al. The revised International Association for the Study of Pain definition of pain: Concepts, challenges, and compromises. Pain. 2020;161(9):1976-82.

4. Siqueira JF, Barnett F. Interappointment pain: Mechanisms, diagnosis, and treatment. Endod Topics. 2004;7(1):93-109.

5. Sathorn C, Parashos P, Messer H. The prevalence of postoperative pain and flare-up in single- and multiple-visit endodontic treatment: A systematic review. Int Endod J. 2008;41(2):91-9.

6. Silva EJNL, Menaged K, Ajuz N, Monteiro MRFP, Coutinho-Filho TS. Postoperative pain after foraminal enlargement in anterior teeth with necrosis and apical periodontitis: A prospective and randomized clinical trial. J Endod. 2013;39(2):173-6.

7. Alsomadi L, Al Habahbeh R. Role of prophylactic antibiotics in the management of postoperative endodontic pain. J Contemp Dent Pract. 2015;16(12):939-43.

8. Ricucci D, Rôças IN, Alves FR, Loghin S, Siqueira JF. Apically extruded sealers: Fate and influence on treatment outcome. J Endod. 2016;42(2):243-9.

9. Zhang W, Peng B. Tissue reactions after subcutaneous and intraosseous implantation of iRoot SP, MTA and AH Plus. Dent Mat J. 2015;34(6):774-80.

10. Almeida LHS, Moraes RR, Morgental RD, Pappen FG. Are premixed calcium silicate-based endodontic sealers comparable to conventional materials? A systematic review of in vitro studies. J Endod. 2017;43(4):527-35.

11. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann T, Mulrow CD, et al. Mapping of reporting guidance for systematic reviews and meta-analyses generated a comprehensive item bank for future reporting guidelines. J Clin Epidemiol. 2020;118:60–8.

12. Maia LC, Antonio AG. Systematic reviews in dental research. A guideline. J Clin Pediatr Dent. 2012;37(2):117–24.

13. Moher D, Shamseer L, Clarke M, Ghersi D, Liberati A, Petticrew M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. Syst Rev. 2015;4:1.

14. Sterne JAC, Savović J, Page MJ, Elbers RG, Blencowe NS, Boutron I, et al. RoB 2: A revised tool for assessing risk of bias in randomized trials. BMJ. 2019;019366:l4898.

15. Higgins JPT, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. BMJ. 2003;327(7414):557-60.

16. Deeks JJ, Higgins JPT, Altman DG (editors). Chapter 10: Analysing data and undertaking meta-analyses. In: Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA (editors). Cochrane Handbook for Systematic Reviews of Interventions version 6.3 (updated February 2022). Cochrane, 2022. Available from www.training.cochrane.org/handbook .

17. Page MJ, Higgins JPT, Sterne JAC. Chapter 13: Assessing risk of bias due to missing results in a synthesis. In: Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA, eds. Cochrane Handbook for Systematic Reviews of Interventions version 6.2 (updated February 2021). Available from www.training.cochrane.org/handbook .

18. Guyatt G, Oxman AD, Akl EA, Kunz R, Vist G, Brozek J, et al. GRADE guidelines: 1. Introduction - GRADE evidence profiles and summary of findings tables. J Clin Epidemiol. 2011;64(4):383-94.

19. Ferreira NS, Gollo EKF, Boscato N, Arias A, Silva EJNL. Postoperative pain after root canal filling with different endodontic sealers: a randomized clinical trial. Braz Oral Res. 2020;34:1-8.

20. Fonseca B, Coelho MS, Bueno CES, Fontana CE, Martin AS, Rocha DGP. Assessment of extrusion and postoperative pain of a bioceramic and resin-based root canal sealer. Eur J Dent. 2019;13(3):343-8.

21. Ates AA, Dumani A, Yoldas O, Unal I. Post-obturation pain following the use of carrier-based system with AH Plus or iRoot SP sealers: A randomized controlled clinical trial. Clin Oral Investig. 2019;23(7):3053-61.

22. Aslan T, Özkan HD. The effect of two calcıum sılıcate-based and one epoxy resın-based root canal sealer on postoperatıve paın: A randomızed controlled trial. Int Endod J. 2021;54(2):190-7.

23. Graunaite I, Skucaite N, Lodiene G, Agentiene I, Machiulskiene V. Effect of resin-based and bioceramic root canal sealers on postoperative pain: A split-mouth randomized controlled trial. J Endod. 2018;44(5):689-93.

24. Drumond JPSC, Maeda W, Nascimento WM, Campos DL, Prado MC, Soares AJ, et al. Comparison of postobturation pain experience after apical extrusion of calcium silicate- and resin-based root canal sealers. J Endod. 2021;47(8):1278-84.

25. Shim K, Jang Y-E, Kim Y. Comparison of the effects of a bioceramic and conventional resin-based sealers on postoperative pain after nonsurgical root canal treatment:

A randomized controlled clinical study. Materials (Basel). 2021;14(10):1-8;

26. Tan HSG, Lim KC, Lui JN, Lai WMC, Yu VSH. Postobturation pain associated with tricalcium silicate and resin-based sealer techniques: A randomized clinical trial. J Endod. 2021;47(2):169-77.

27. Khandelwal A, Jose J, Teja K-V, Palanivelu A. Comparative evaluation of postoperative pain and periapical healing after root canal treatment using three different base endodontic sealers – A randomized control clinical trial. J Clin Exp Dent. 2022;14(2):e144-e152.

28. Kim J-H, Cho S-Y, Choi Y, Kim D-H, Shin S-J, Jung I-Y. Clinical efficacy of sealer-based obturation using calcium silicate sealers: A randomized clinical trial. J Endod. 2022;48(2):144-51.

29. Paz A, Vasconcelos I, Ginjeira A. Evaluation of postoperative pain after using bioceramic materials as endodontic sealers. EC Dent Sci. 2018;17:1739-48.

30. McGuinness LA, Higgins JPT. Risk-of-bias VISualization (robvis): An R package and Shiny web app for visualizing risk-of-bias assessments. Res Syn Methods. 2020;12(1):55-61.

31. Riccuci D, Langeland K. Apical limit of root canal instrumentation and obturation, part 2. A histological study. Int Endod J. 1998;31(6):394-409.

32. Jamali S, Darvish M, Nasrabadi N, Jafarizadeh S. Evaluation of the effect of the intensity and occurrence of postoperative pain of resin-based and bioceramic root canal sealers: A systematic review and meta-analysis of randomized controlled trial studies. Pesqu Bras Odontopediatria Clín Integr. 2021;21(2):e0219.

33. Junior ECS, Vieira WA, Normando AGC, Pereira JV, Ferraz CCR, Almeida JFA, et al. Calcium Silicate-based sealers do not reduce the risk and intensity of postoperative pain after root canal treatment when compared with epoxy resin-based sealers: A systematic review and meta-analysis. Eur J Dent. 2021;15(2):347-59.

34. Mekhdieva E, Del Fabbro M, Alovisi M, Comba A, Scotti N, Tumedei M, et al. Postoperative pain following root canal filling with bioceramic vs. traditional filling techniques: A systematic review and meta-analysis of randomized controlled trials. J Clin Med. 2021;10(19):4509.

35. Chopra V, David G, Baysan A. Clinical and radiographic outcome of non-surgical endodontic treatment using calcium silicate-based versus resin-based sealers—A systematic review and meta-analysis of clinical studies. J Funct Biomater. 2022;12(2):38.

36. Ali SG, Mulay S, Palekar A, Sejpal D, Joshi A, Gufran H. Prevalence of and factors affecting post-obturation pain following single visit root canal treatment in Indian population: A prospective, randomized clinical trial. Contemp Clin Dent. 2012;3(4):459-63.

37. Alí A, Olivieri JG, Duran-Sindreu F, Abella F, Roig M, García-Font M. Influence of preoperative pain intensity on postoperative pain after root canal treatment: a prospective clinical study. J Dent. 2016;45:39-42.

38. Alaçam T, Tinaz AC. Interappointment emergencies in teeth with necrotic pulps. J Endod. 2002;28(5):375-7.

39. Siqueira JF, Rôças IN, Favieri A, Machado AG, Gahyva SM, Oliveira JCM, et al. Incidence of postoperative pain after intracanal procedures based on an antimicrobial strategy. J Endod. 2002;28(6):457-60.

40. Cintra LTA, Benetti F, Queiroz IOA, Ferreira LL, Massunari L, Bueno CRE, et al. Evaluation of the cytotoxicity and biocompatibility of new resin epoxy–based endodontic sealer containing calcium hydroxide. J Endod. 2017;43(12):2088-92.

41. Lee JK, Kim S, Lee S, Kim H-C, Kim E. In vitro comparison of biocompatibility of calcium silicate-based root canal sealers. Materials. 2019;12(15):2411.

42. Zhang W, Li Z, Peng B. Ex vivo cytotoxicity of a new calcium silicate-based canal filling material. Int Endod J. 2010;43(9):769-74.

43. Benetti F, Queiroz IOA, Oliveira PHC, Conti LC, Azuma MM, Oliveira SHP, et al. Cytotoxicity and biocompatibility of a new bioceramic endodontic sealer containing calcium hydroxide. Braz Oral Res. 2019;33:1-9.

44. Silva ECA, Tanomaru-Filho M, Silva GF, Delfino MM, Cerri PS, Guerreiro-Tanomaru JM. Biocompatibility and bioactive potential of new calcium silicate-based endodontic sealers: Bio-C Sealer and Sealer Plus BC. J Endod. 2020;46(10):1470-7.

45. Guyatt GH, Oxman AD, Vist G, Kunz R, Brozek J, Alonso-Coelho P, et al. GRADE guidelines: 4. Rating the quality of evidence-study limitations (risk of bias). J Clin Epidemiol. 2011;64(4):1283–93.

46. Guyatt GH, Oxman AD, Kunz R, Woodcock J, Brozek J, Helfand M, et al. GRADE guidelines: 7. Rating the quality of evidence-inconsistency. J Clin Epidemiol. 2011;64(12):1294–1302.

47. Guyatt GH, Oxman AD, Kunz R, Woodcock J, Brozek J, Helfand M, et al. GRADE guidelines: 8. Rating the quality of evidence-indirectness. J Clin Epidemiol. 2011;64(12):1303–10.

48. Guyatt GH, Oxman AD, Kunz R, Brozek J, Alonso-Coelho P, Rind D, et al. GRADE guidelines: 6. Rating the quality of evidence— imprecision. J Clin Epidemiol. 2011;64(12):1283-93.

49. Guyatt GH, Oxman AD, Sultan S, Glasziou P, Akl EA, Alonso-Coelho P, et al. GRADE guidelines: 9. Rating up the quality of evidence. J Clin Epidemiol. 2011;64(12):1311–6.