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The Effect of Number of Visits, Use of Solvent and Gutta-percha Removal Technique on Postoperative Pain following Nonsurgical Endodontic Retreatment; A Systematic Review and Meta-analysis

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Introduction: The nonsurgical endodontic retreatment (NERT) is the first choice of dental ministration when primary/initial endodontic treatment fails. The present study aimed to investigate the presence of postoperative pain (POP) after NERT in permanent asymptomatic teeth as well as possible factors associated with POP. **Materials and Methods:** A comprehensive search of literature was performed in Pubmed/MEDLINE, Embase, Scopus and Web of Science databases, up to January 2023; including randomized clinical trials and prospective studies. The risk of bias was assessed with RoB 2.0 and ROBINS-I tools. Subgroups analyses were conducted to evaluate the differences in the incidence or level of POP between the number of visits, the use/not use of solvent, the removal technique of gutta-percha, and the period of POP analysis. Mean differences and confidence intervals (CI) of 95% were used as measures of effect, and meta-regression was used along with subgroup analysis. The certainty of evidence was assessed using GRADE, and the probability value of <0.05 was considered significant. **Results:** Twenty-four studies were selected, with thirteen included in the meta-analysis. There was a statistical difference between the incidence of POP after 24 h (95% CI, 0.28 to 0.52) and one week (95% CI, 0.02 to 0.13) from the endodontic retreatment (P<0.01). However, there was no statistical difference between different techniques, number of visits and use of solvent (P>0.05) in the same period. In addition, the certainty of evidence was very low. **Conclusions:** Post-operative pain is a common response to NERT, independent of the retreatment technique(s) applied, number of visits and use of solvent(s); with very low certainty of evidence as well as low risk of bias. Moreover, the current analysis showed a (very) serious risk of inconsistency and imprecision. However, POP was significantly reduced within 1 week of the NERT.

Keywords: Endodontics; Endodontic Retreatment; Meta-analysis; Postoperative Pain; Systematic Review

Introduction

One of the main objectives of an endodontic treatment is to prevent or treat apical periodontitis (AP), which may be achieved using different techniques that can (i) avoid contamination in vital pulpal tissues and (ii) lead to the reduction of microorganisms within the root canal system in dental pulp necrosis [1]. However, failure in endodontic treatment(s) has been reported to occur in 7%-18% of teeth; depending upon previous clinical condition(s) as well as pulp and periapical diagnosis [2].

The most likely cause of failure in primary endodontic treatment(s) is the persistence of infection inside the root canal system; often accompanied by the presence of AP. The post-treatment AP can be managed by non-surgical retreatment, peri-radicular surgery or tooth extraction [1, 3]. The non-surgical endodontic retreatment (NERT) is the first and foremost treatment option; specifically since it is considered a simple therapy and less invasive with benefits proven by the literature [4-6]. Technological developments in dentistry (*e.g.* the use of operating microscopes or employment of loupes, which have enhanced visualization beside the introduction of rotary endodontic instruments) may improve the success rate of non-surgical endodontic retreatments [7]. In cases where teeth cannot be treated with NERT, or when retreatment seems ineffective, not feasible or contraindicated,

surgical endodontic retreatment is recommended [6]. Several factors during NERT have been investigated in the literature; type of irrigants [8], number of visits [9], intracanal dressings [10], instrumentation techniques [11], endodontic sealers [12], intracanal solvents [13] and other supporting therapies [14, 15].

Factors such as disinfection [16], effectiveness in removing gutta-percha [17] and POP [18] are extensively evaluated to compare the most beneficial retreatment techniques. Postoperative pain results from acute inflammation in the peri-radicular tissue and thus, can be an expected consequence for the corresponding treatment [9] . Moreover, POP after the endodontic retreatment appears to be distressing for the patient; especially in cases of previously asymptomatic teeth [19](19). According to Jariwala and Goel [20], pain relief is often more important than successful endodontic therapy for patients. AlRahabi [21] has reported that the prevention and management of POP after nonsurgical endodontic treatment are the main components of successful outcomes. If practitioners warn patients that postoperative pain is common and/or expected, the communication with patient(s) becomes easier, and improves patients' confidence and their perspective over future dental treatments [21-23].

It is of great relevance for the endodontic community to realise whether different approaches, techniques and materials are capable of interfering in POP. To the best of authors' knowledge, several clinical studies have been conducted; nevertheless, there is still no systematic literature review that has compiled all the relevant information. Therefore, the purpose of the present systematic review and meta-analysis was to investigate the post-operative pain after nonsurgical endodontic retreatment in permanent and asymptomatic teeth, next to possible factors associated with POP.

Materials and Methods

Protocol and registration

The protocol of the current systematic review and meta-analysis was registered in PROSPERO, an international prospective register of systematic reviews (CRD42020178448). This study was conducted and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines.

Participant-Intervention-Comparison-Outcomes-Study design (PICOS) question

The present systematic review and meta-analysis were conducted to answer the focused review question, "Do the number of visits, use of solvent and removal technique of gutta-percha affect postoperative pain after nonsurgical endodontic retreatment?", according to the following PICOS elements:

- Participant: patients with teeth having the indication for NERT.
- Intervention: nonsurgical endodontic retreatment.
- Comparison: number of visits, use of solvent and removal technique of gutta-percha.
- Outcomes: postoperative pain.
- Study design: randomized controlled trials (RCTs) and prospective studies.

Search strategy

The original articles included in the present systematic review and meta-analysis were obtained through search in Pubmed/MEDLINE, Embase, Scopus and Web of Science databases, up to January 2023. In addition, the "Medical Subject Heading" (MeSH) terms and keywords for POP and endodontic retreatment, and their combinations were used for the search, according to each database. No language and publication year restrictions were applied. The search results of various databases were cross-checked to find and remove duplicates.

Eligibility criteria and selection of the studies

Randomized controlled trials and prospective studies, which evaluated POP after NERT, were included. Studies conducted in patients with *(i)* symptomatic teeth, *(ii)* permanent teeth with open apices, *(iii)* primary teeth, *(iv)* with drop out >30%, and *(v)* with full text not available were excluded. Two reviewers (GS, IS) independently screened the abstracts, and full-text articles were only selected in the electronic search. If there was a disagreement between reviewers, consensus was achieved. To ensure inter-rater reliability, the Cohen's kappa coefficient was calculated; 0.78 for the evaluation of inclusion criteria and 0.87 for exclusion criteria.

Data extraction and Risk of bias of individual studies

The data were extracted and the risk of bias was assessed independently by the same reviewers of electronic search (GS, IS) with a protocol defined for data extraction. The primary outcome of interest was the POP after NERT. The incidence of POP and intensity data shown in the included studies were collected. Furthermore, author, year of publication, country, study design, sample size, number of visits, use of solvent, removal technique of gutta-percha, prescription for analgesics, measures of outcome, follow-up and conclusions were extracted from the publications.

To assess the risk of bias for RCTs and prospective studies, RoB 2.0 and ROBINS-I tools *via* "Cochrane Handbook for Systematic Reviews of Interventions"[24] were used, respectively. The above-mentioned tools consider specific domains according to the methodological characteristics of the studies evaluated. Each study was categorized as low, unclear or high risk of bias. The Cohen's kappa coefficient for inter-investigator agreement of the risk of bias assessment was calculated at 0.83.

Table 1. Characteristics of included studies

Author	Country	Intervention Group	Sample size	Number of visits	Solvent use	Gutta-percha removal technique	Pain scale	Authors conclusions
Imura and Zuolo [25]	Brazil	-	415	1 and 2	Xylol	Manual	-	Independent of the number of appointments, the main factor in minimizing the risk of flare-ups is careful cleaning and shaping the canal system
Siqueira Jr *et al.* [26]	Brazil	Necrotic pulps or retreatment	627 teeth=499 necrotic pulp, 120 asymptomatic retreatment and 8 symptomatic retreatment	2	Eucalyptol	Manual	No pain; mild pain; moderate pain; severe pain	The use of an antimicrobial strategy can significantly remove microorganisms from the root canal and theoretically prevent postoperative pain
Yoldas *et al.* [27]	Turkey	Single-versus two-visit treatment	218 teeth=73 1-visit asymptomatic, 79 2-visit asymptomatic, 33 1-visit symptomatic, 33 2-visit symptomatic	1 and 2	-	Manual associated with automatized	No pain; mild pain; moderate pain; severe pain	2-visit endodontic retreatment reduces postoperative pain in endodontically retreated symptomatic teeth and decreases the number of flare-ups in all retreatment cases compared to 1-visit endodontic retreatment
Gotler *et al.* [28]	Israel	Necrotic or vital pulps or retreatment	274=141 vital pulp, 52 necrotic pulp, 8 retreatment	1	Xylene	Manual	Continuous 1–5 point scale (1: no pain, 2: mild pain, 3: moderate pain, 4: severe pain and 5: very severe/ unbearable pain)	Teeth with vital pulp presented a significantly higher incidence and intensity pain
Topçuoğlu [29]	Turkey	Gutta-percha removal technique	130 teeth=43 manual, 87 automatized	2	Eucalyptol	Manual or automatized	Visual analogue scale:1–no pain; 2–slight pain; 3–moderate pain; and 4–severe pain	Removal of root canal filling material using hand files caused greater postoperative pain in patients having upper incisor teeth in specified time intervals during the first two days
Uyan *et al.* [30]	Turkey	Single- versus two-visit treatment	78 teeth=20 1-visit and 58 in two-visit[29]	1 and 2	-	Manual associated with automatized	An 170-mm Heft-Parker visual analogue scale	The used of an antimicrobial intracanal dressing remains a recommended method for eliminating postoperative pain after retreatment cases
Grunaite *et al.* [31]	Lithuanian	Resin-based and Bioceramic Root Canal Sealers	114 teeth=57 Resin-based Root Canal Sealer and 57 Bioceramic Root Canal Sealer	1	-	Manual associated with automatized	Visual analogue scale consisting of a 100-mm-long line divided into 10 equal intervals from 0 (no pain) to 100 (very severe pain)	The sealers performed similarly in terms of occurrence and intensity of postoperative pain
Erdem Hepsenoglu *et al.* [9]	Turkey	Single- versus two-visit treatment	150 teeth=50 1-visit and 100 in two-visit	1 and 2	-	Manual associated with automatized	Verbal rating scale with well-defined categories: 1–no pain; 2–slight pain; 3–moderate pain; and 4–severe pain	The postoperative pain incidence in single-visit endodontic retreatments was less than that in multiple-visit endodontic retreatments

Eyuboglu & Özcan [32]	Turkey	Different nickel-titanium shaping systems	99 teeth=33 OneShape, 33 Revo-S, 33 WaveOne	1	-	Manual associated with automatized	Four-level verbal rating scale, where 0 indicated no pain, 1 indicated slight pain, 2 indicated moderate pain, and 3 indicated severe pain	The postoperative pain using shaping instruments based on a rotational approach was less than those based on a reciprocal approach
Genc Sen and Kaya [33]	Turkey	Disinfection with a 940-nm diode laser	73 teeth=36 pseudo-laser disinfection and 37 laser disinfection	1	-	Manual associated with automatized	An 11-item numeric rating scale (NRS) for pain assessment	The used of a 940-nm diode laser can efficiently reduce pain and provide comfort to the patient after endodontic retreatment
Genc Sen *et al.* [34]	Turkey	Solvent use	88 teeth=43 non-solvent use and 45 solvent use	1	Eucalyptol-based solvent	Manual associated with automatized	An 11-item numeric rating scale (NRS) for pain assessment	The use of a gutta-percha solvent during the removal of root canal filling did not result in a significant reduction in postoperative pain
Çanakçi *et al.* [35]	Turkey	Different nickel-titanium shaping systems	180 teeth=45 Protaper, 45 Hyflex EDM, 45 Reciproc Blue, 45 WaveOne Gold	1	-	Manual associated with automatized	An 11-level numeric rating scale	Using four different rotary or reciprocating NiTi systems during root canal retreatment did not result in a significant difference in postoperative pain or analgesic intake.
Spohr *et al.* [36]	Brazil	Gutta-percha removal technique	48 teeth=24 Manual, 24 Reciproc	2	Eucalyptol-based solvent	Manual or automatized	An 11-item numeric rating scale (NRS)	Manual and reciprocating instruments achieved the same results regarding the prevalence and intensity of postoperative pain and analgesic intake
İnce-Yusufoğlu *et al.* [37]	Turkey	Activation techniques	90 teet=45 EDDY activation, 45 manual dynamic activation	1	-	Manual associated with automatized	A 10-point numerical rating scale (NRS)	Pain intensity and frequency after a single non-surgical retreatment session were lesser in the MDA group than the EDDY group, with no difference in PP within the first week after non-surgical retreatment.

Statistical analysis

The studies included were divided into three groups for statistical analysis: (a) studies that showed the incidence of POP 24 h after retreatment, (b) studies that showed the incidence of POP one week after retreatment, and (c) studies that showed the intensity of POP 24 h after retreatment. Additionally, studies that simultaneously showed incidence and intensity were included in both groups. Besides, some studies were divided based on their tested intervention, according to Tables 1 and 3. In each group, subgroup analysis and meta-regression were conducted. For the studies that showed the intensity of POP 24 h after retreatment, the POP was measured on a variety of pain scales. For meta-analysis, the intensity of POP was converted in a same scale of 0 -10 mm. Data were combined using a random-effects model (RStudio, Boston, MA, US). Mean differences and confidence intervals of 95% (CI=95%) were used as measures of effect. Heterogeneity was assessed with test of heterogeneity; I^2 (level of inconsistency) and Tau^2/R^2 (estimate of between-study variance) statistics.

To evaluate the differences in the estimate of effect between the number of visits (single-visit or multiple-visit), the use (or not use) of solvent, the removal technique of gutta-percha (manual or manual/automatized), and the period of analysis of POP (24 h or one week after the NERT), subgroup analysis was planned. The Meta package, titled, "General Package for Meta-Analysis, version: 4.12-0, Guido Schwarzer" was used for the analysis. The meta-regression was performed along with subgroup analysis to identify the possible sources of heterogeneity. The Metafor package titled "Meta-AnalysisPackageforR,version:2.4-0,Wolfgang Viechtbauer"

Table 2. List of excluded articles in addition to reason(s) for exclusion

Author, Year	Title	Reason for exclusion
Trope M 1990	Relationship of intracanal medicaments to endodontic flare-ups	The sample included patients with symptomatic teeth
Trope M 1991	Flare-up rate of single-visit endodontics	
Kvist T, Reit C 2000	Postoperative discomfort associated with surgical and nonsurgical endodontic retreatment	Drop out >30%
Kvist T 2001	Endodontic retreatment. Aspects of decision making and clinical outcome	
Mattscheck DJ, Law AS, Noblett WC 2001	Retreatment versus initial root canal treatment: factors affecting posttreatment pain	The sample included patients with symptomatic teeth
Glennon, JP; Ng, YL; Setchell, DJ; *et al.* 2004	Prevalence of and factors affecting postpreparation pain in patients undergoing two-visit root canal treatment	
Yoo YJ, Shon WJ, Baek SH, *et al.* 2014	Effect of 1440-nanometer neodymium:yttrium-aluminum-garnet laser irradiation on pain and neuropeptide reduction: a randomized prospective clinical trial	
Eyuboglu TF, Olcay K, Özcan M 2017	A clinical study on single-visit root canal retreatments on consecutive 173 patients: frequency of periapical complications and clinical success rate	
Arslan H, Doğanay E, Karataş E, *et al.* 2017	Effect of Low-level Laser Therapy on Postoperative Pain after Root Canal Retreatment: A Preliminary Placebo-controlled, Triple-blind, Randomized Clinical Trial	
Fazlyab M, Shahmirzadi SE, Esnaashari E, *et al.* 2021	Effect of low-level laser therapy on postoperative pain after single-visit root canal retreatment of mandibular molars: A randomized controlled clinical trial	
Fahim MM, Saber SEM, Elkhatib WF, *et al.* 2022	The antibacterial effect and the incidence of post-operative pain after the application of nano-based intracanal medications during endodontic retreatment: a randomized controlled clinical trial	
Asnaashari M, Ashraf H, Daghayeghi AH, *et al.* 2017	Management of Post Endodontic Retreatment Pain With Low Level Laser Therapy	The sample included patients with symptomatic teeth
Comparin D, Moreira EJL, Souza EM, *et al.* 2017	Postoperative Pain after Endodontic Retreatment Using Rotary or Reciprocating Instruments: AÂ Randomized Clinical Trial	
Garcia-Font M, Durán-Sindreu F, Morelló S, *et al.* 2018	Postoperative pain after removal of gutta-percha from root canals in endodontic retreatment using rotary or reciprocating instruments: a prospective clinical study	
Brignardello-Petersen 2018	Low-level laser therapy may reduce postoperative pain levels after root canal retreatment in patients with low preoperative pain levels	

Table 3. Incidence and mean intensity of postoperative pain after nonsurgical endodontic retreatment of the included studies

Author	Period of analysis	Incidence	Mean Intensity (scale)
Siqueira Jr *et al.* [26]	One week	13,3%	-
Yoldas *et al.* [27]	One week	18.4%	-
Gotler *et al.* [28]	24 hours	44.4%	1.81 (1-5)
Topçuoğlu and Topçuoğlu [29]	24 hours	33.8%	-
Topçuoğlu and Topçuoğlu [29]	One week	0%	-
Uyan *et al.* [30]	24 hours	-	53.24 (0-170)
Grunaite *et al.* [31]	24 hours	19.2%	3.86 (0-100)
Grunaite *et al.* [31]	One week	0%	-
Erdem Hepsenoglu *et al.* [9]	24 hours	58%	-
Erdem Hepsenoglu *et al.* [9]	One week	12.6%	-
Eyuboglu and Özcan [32]	24 hours	68.6%	-
Eyuboglu and Özcan [32]	One week	16,1%	-
Genc Sen and Kaya [33]	24 hours	-	2.09 (0-10)
Genc Sen *et al.* [34]	24 hours	-	1.88 (0-10)
Çanakçi *et al. [35]*	24 hours	-	3.3 (0-10)
Spohr *et al.* [36]	24 hours	14,5%	0.33 (0-10)
Spohr et al. [36]	One week	2,08%	0.0 e 0.8 (0-10)
Spohr *et al.* [36]	24 hours	4,16%	0.04 (0-10)
Spohr *et al.* [36]	One week	2,08%	0.0 e 0.04 (0-10)
İnce-Yusufoğlu *et al.* [37]	24 hours	56%	3.04 (0-10)
İnce-Yusufoğlu *et al.* [23]	One week	5.6%	2.47 (0-10)

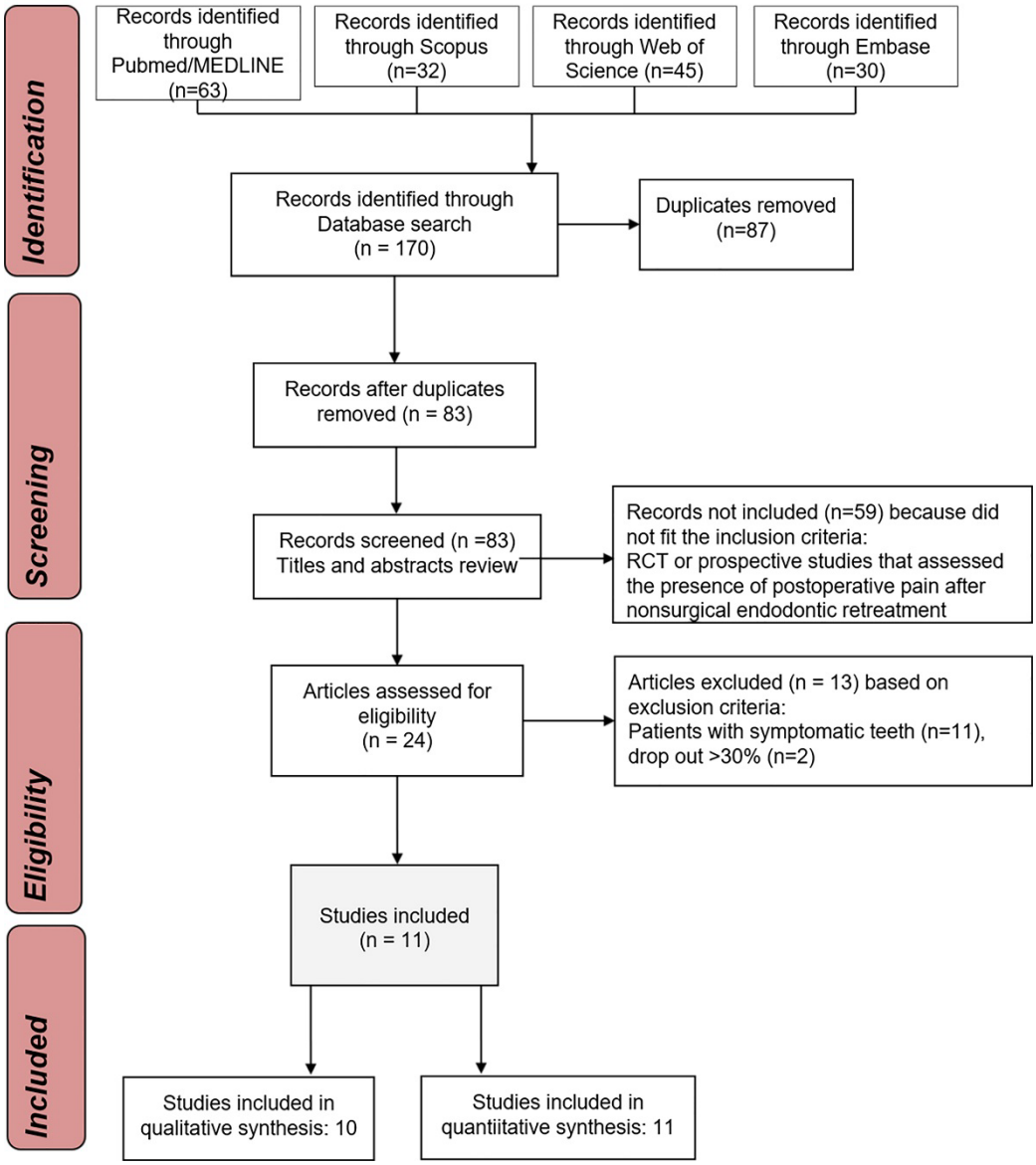

Figure 1. Schematic flow diagram representing study inclusion

was used for the analysis. Software "RStudio, version 1.2.5042 (RStudio Inc., Boston, MA, USA)" was used, and the significance level adopted was set at 5%.

Assessment of the certainty of evidence

The certainty of evidence was assessed using the Grading of Recommendations Assessment, Development and Evaluation (GRADE). The aforementioned system uses the number of studies, study design, risk of bias, inconsistency, indirectness of evidence, imprecision and other considerations to assess the certainty of evidence. Moreover, the certainty of evidence can be classified to very low, low, moderate and high. The assessment was conducted independently by the two reviewers (GS, IS), and consensus was achieved if there was a disagreement between reviewers. This analysis was performed for each outcome assessed; incidence of POP 24 hours and one week after retreatment, and intensity of POP 24 hours after retreatment. Only the studies included in the meta-analysis were used for this analysis.

For the assessment conducted in the current investigation, the certainty of evidence was downgraded for one level if more than 50% of the studies included showed a high risk of bias. In relation to inconsistency, if the studies had no overlap of 95% CI, and the tests of heterogeneity showed $P<0.05$ and $I^2 > 75\%$, the certainty of evidence was downgraded for two levels. However, if only one of these parameters was observed; only one level was downgraded. In addition, if the included studies showed different sample characteristics of PICOS question population, the certainty of evidence was downgraded for one level.

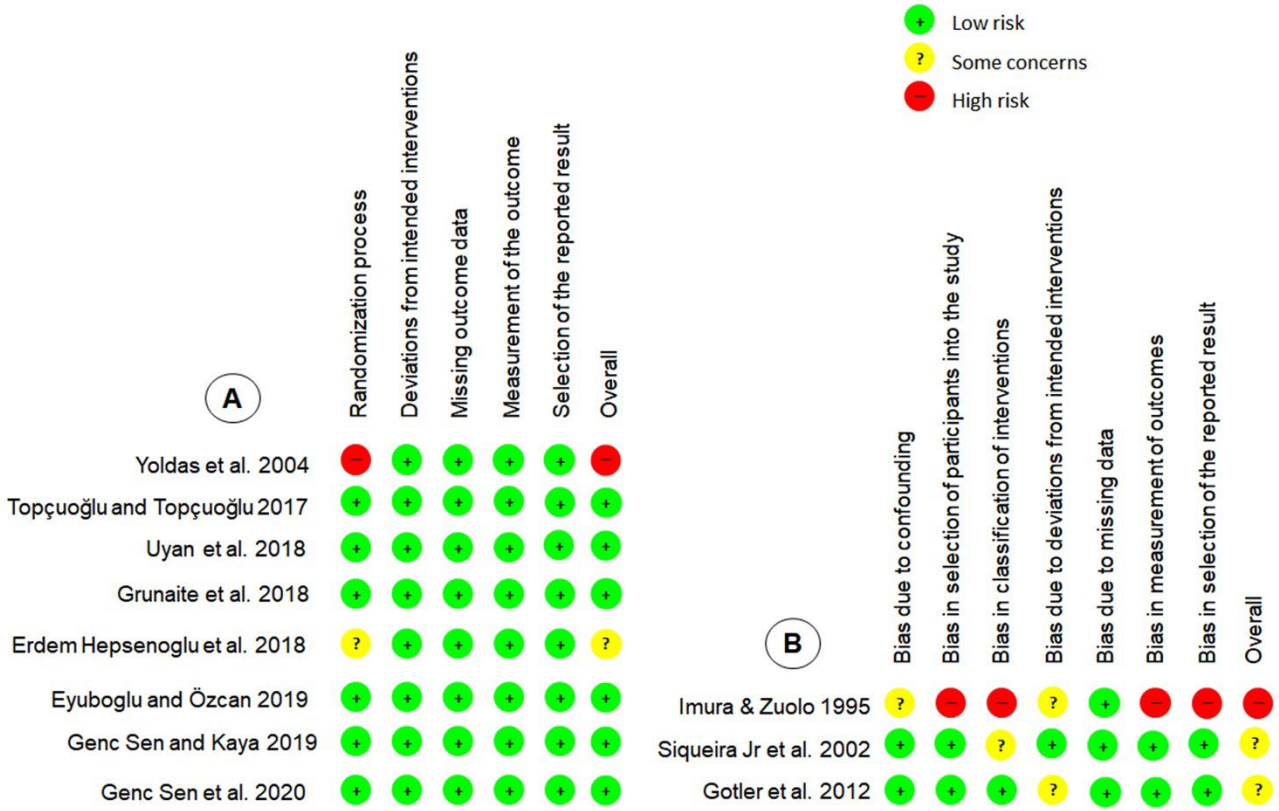

Figure 2. Risk of bias summary; in *A*) Randomized clinical trials, in *B*) Prospective studies

The "Optimal Information Size Guidelines" were considered for imprecision. When analysis showed the incidence of POP, if the total of events was less than 300, the certainty of evidence was downgraded for one level. Similarly, when studies showed incidence of POP, if the total of events was less than 400, the certainty of evidence was downgraded for one level.

Results

Study selection

Figure 1 shows the flow diagram of the current investigation. From the initial 213 potentially relevant articles identified by the electronic search, 113 were removed because they were duplicates. Titles and abstract of 100 papers were evaluated, and 71 were not included. The main reason for exclusion was the fact that the studies did not fit the inclusion criteria: RCT or prospective studies that assessed POP after nonsurgical endodontic retreatment. The 29 articles remained were fully analyzed to assess eligibility; however, 15 were excluded because they included patients with symptomatic teeth, including two articles which were excluded because they had a drop out > 30%. Therefore, 14 studies were chosen to be included in the systematic review and 13 in the meta-analysis. Table 2 depicts the list of excluded articles and the reason(s) for exclusion.

Data collection

All the selected studies were published in English. Eleven studies were randomized. One study had a split-mouth design [9, 27, 29-37] and tested experimental; controlling POP in the same patient. Three studies were prospective investigations [25, 26, 28]. As their primary outcome, the selected studies had POP, which was measured on a variety of time periods. Characteristics of the included studies are summarized in Table 1.

Nonsurgical endodontic retreatment was performed in a single-visit in eleven studies [9, 25, 27, 28, 30-35, 37], and two visits in seven studies [9, 25-27, 29, 30, 36]. The study by Imura and Zuolo [25] considered only severe pain and, thus, was not pooled in the meta-analysis. Furthermore, the period of analysis for POP assessment was not clear.

Solvent was used in six studies; nevertheless, only one study evaluated its effect on POP after nonsurgical endodontic retreatment [34]. Xylol, Eucalyptol and Xylene were the solvents used in the studies by Imura and Zuolo [25], Siqueira Jr *et al.*[26], Gotler *et al.* [28], Topçuoğlu and Topçuoğlu [29], Genc Sen *et al.* [34] and Spohr *et al.* [36]. Furthermore, only in five

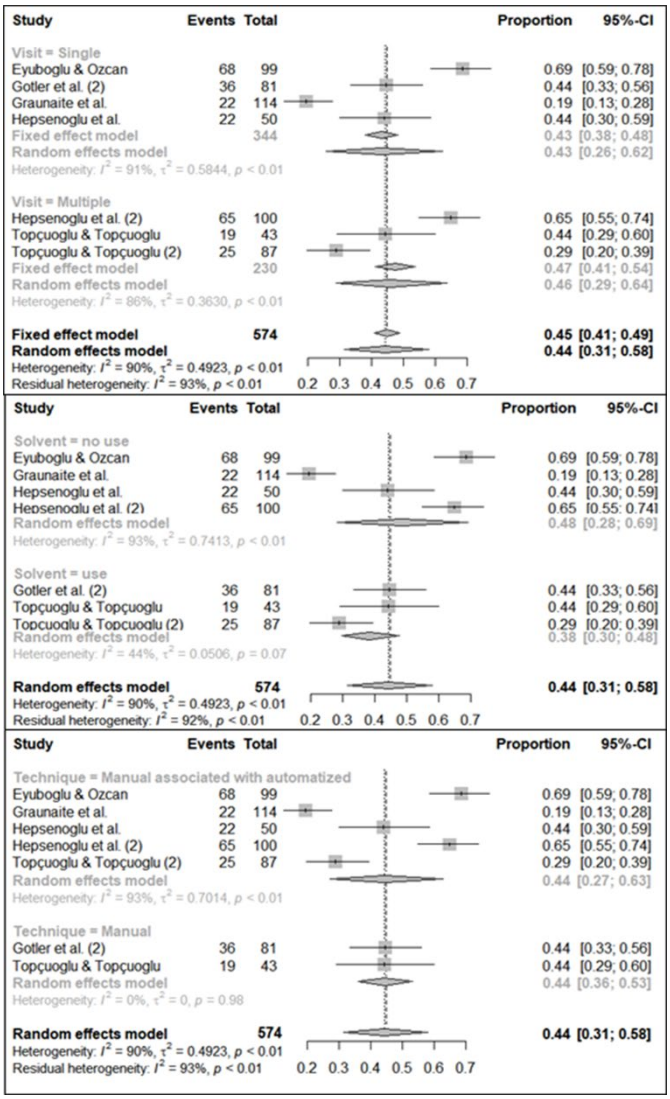

Figure 3 Forest plot for subgroup analysis of studies that showed the intensity of postoperative pain 24 hours after nonsurgical endodontic retreatment

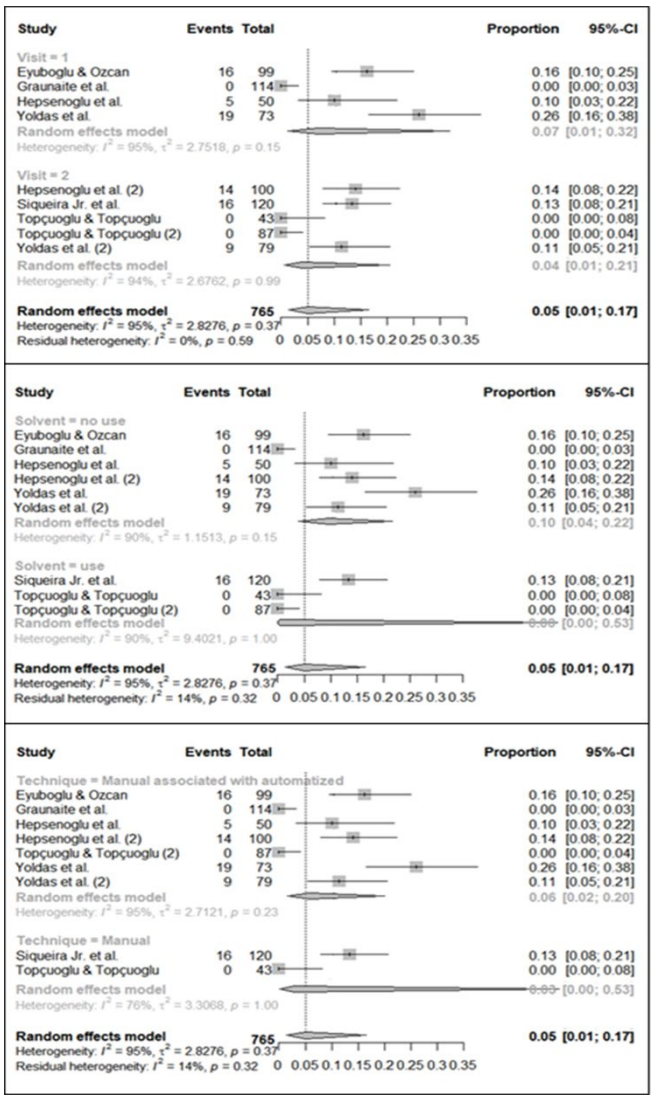

Figure 4. Forest plot for subgroup analysis of studies that showed the incidence of postoperative pain one week after nonsurgical endodontic retreatment

studies, the gutta-percha removal was made with hand instruments, while in nine studies, hand files were associated with automatized instruments. Only in the studies conducted by Topçuoğlu and Topçuoğlu [29] and Spohr *et al.* [36], the effect of gutta-percha removal technique (manual or automatized) on POP after nonsurgical endodontic retreatment was evaluated.

The level of discomfort assessed was rated on *(i)* no pain, *(ii)* mild pain, *(iii)* moderate pain, and *(iv)* severe pain in five studies [9, 26, 27, 29, 32]. In the study by Topçuoğlu and Topçuoğlu [29], a visual analogue scale (VAS) was used whereas in the studies by Erdem Hepsenoglu *et al.* [9], Eyuboglu and Özcan [32], a verbal rating scale (VRS) was considered. In the studies by Siqueira Jr *et al.* [26] and Yoldas *et al.* [27], patients were asked about the occurrence of POP based on the four levels of pain. However, Gotler *et al.* [28] used a continuous 1–5 point scale (1: no pain, 2: mild pain, 3: moderate pain, 4: severe pain and 5: very severe/unbearable pain) to assess POP. In the study by Uyan *et al.*[30], a 170-mm Heft-Parker VAS was used whilst in the studies by Grunaite *et al.*, a VAS was applied; consisting of a 100-mm-long line divided into 10 equal intervals from 0 (no pain) to 100 (very severe pain) [31]. Genc Sen and Kaya [33], Genc Sen *et al.* [34], Çanakçi *et al.* [35], Spohr *et al.* [36] and İnce-Yusufoğlu *et al.* [37] considered an 11-item numeric rating scale (NRS) for the assessment of pain. Table 3 shows the mean intensity and incidence of POP after NERT of the included studies.

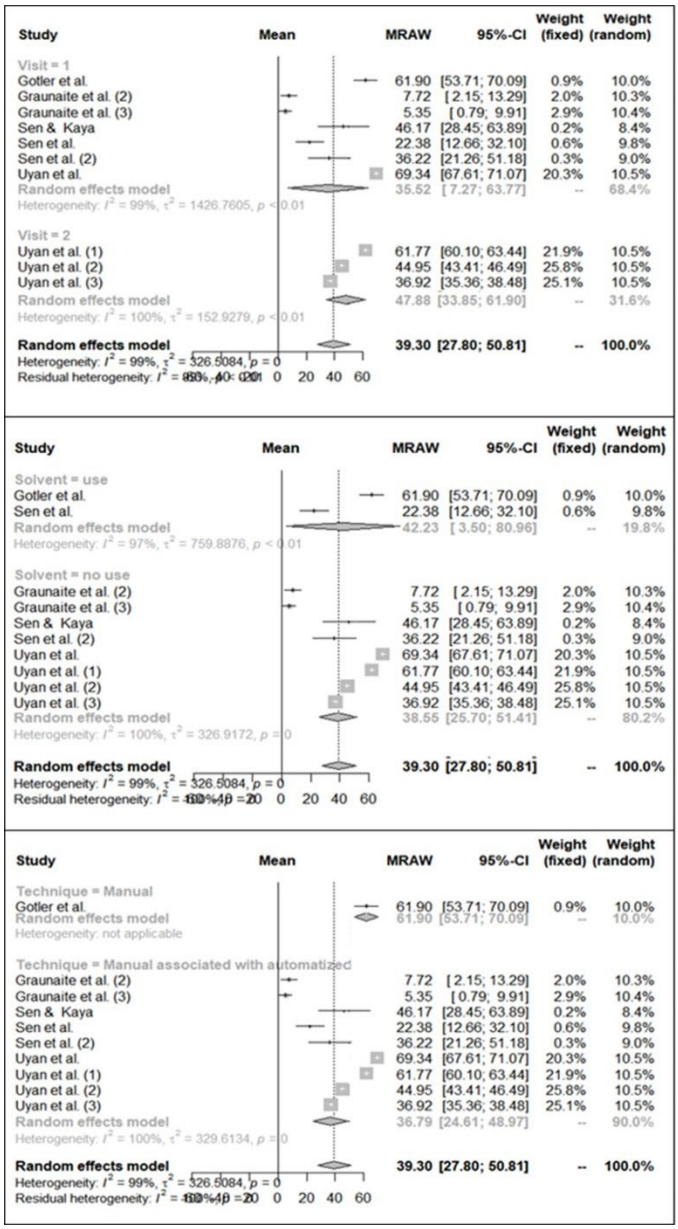

Figure 5. Forest plot for subgroup analysis of studies that showed the incidence of postoperative pain 24 hours after nonsurgical endodontic retreatment

Risk of bias

Figure 2 shows the assessment of the risk of bias regarding the studies included. Only one RCT and one prospective study had an overall high risk of bias. In the RCT, the randomization process of study was unclear. In the prospective study, the selection of patients as well as their interventions were not specified, and the measurement of outcome was unclear. In addition, three studies had concerns: one RCT study; because the randomization process was not detailed, and two prospective studies; because the classification of intervention and the intended intervention were not correctly defined. Finally, six RCTs had an overall low risk of bias.

Meta-analysis

The study by Imura and Zuolo [25] was not included for meta-analysis because the data provided was incomplete. The number of visits, use of solvent(s) and removal technique of gutta-percha did not result in significant differences of incidence/intensity of pain (P>0.05) (Figures 3–5). The majority of the subgroups analysis showed a high heterogeneity (P<0.05 and I^2>75%). The subgroups did not change the estimative effect. Moreover, the included studies demonstrated that the POP measurement period (24 h or one week after NERT) showed a difference in the estimate of effect (P<0.0001). When the mensuration was performed 24 h following the retreatment (CI=95%, −0.28 to 0.52), the incidence of POP was greater after one week (CI=95%, −0.02 to 0.13) (Figure 6). The subgroups analysis showed a high heterogeneity (P-value<0.05 and I^2>75%).

The meta-regression showed that the number of consults, study design, and gutta-percha removal technique failed to explain the heterogeneity of the results concerning the pain outcome (Tables 4 & 5). The use of solvent helped explain most of the heterogeneity of the pain level (R^2 23.9%). The meta-regression was performed with different conversions of pain scales; however, it also failed to explain the heterogeneity of the pain level (R^2 0%) (Table 5).

Certainty of evidence

Table 6 shows the assessment of certainty of evidence. More than 50% of studies included showed a low risk of bias. Therefore, and in order to assess the certainty of evidence, the risk of bias was not considered significant. The result showed a significant problem of inconsistency; due to no overlapping of IC=95% and tests of heterogeneity showing P<0.05 and I^2>75%. On indirectness of evidence, all studies included showed eligibility criteria in which populations had equal characteristics compared to the population of research question. Furthermore, the evaluation of publication bias and possible confounder did not increase the level of certainty of evidence; because the studies showed high heterogeneity and the gray literature was not used for the selection of studies.

Discussion

Postoperative pain is one of the major concerns that affect patients and endodontists during and after endodontic procedures. The included studies in the present systematic review showed that the incidence of POP varied from 4.16% to 68.6% in 24 hours, and from 0% to 18.4% in one week after endodontic retreatment. Many professionals still have doubts if different techniques and materials can affect POP. There is still a gap of knowledge in the literature regarding the effect(s) of variables of endodontic retreatment on the prognosis of POP. According to the findings of the current systematic review and

Table 4. Effects of potential factors affecting the heterogeneity for pain incidence, calculated with meta-regression

Study group	Subgroup	I^2	tau^2
Incidence of postoperative pain 24hours after retreatment	Number of consults	89.6	0.54
	Use of solvent	88.7	0.49
	Gutta-percha removal technique	89.3	0.48
	Study	89.4	0.53
Incidence of postoperative pain one week after retreatment	Number of consults	91.1	1.79
	Use of solvent	89.2	1.45
	Gutta-percha removal technique	92.8	2.16
	Study	90.6	1.76

Table 5. Effects of potential factors affecting the heterogeneity for pain intensity, calculated with meta-regression

Study group	Subgroup	I^2	R^2
Intensity of postoperative pain 24 hours after retreatment	Number of consults	99.5	9.5
	Use of solvent	99.4	23.9
	Gutta-percha removal technique	99.5	0
	Scale	99.5	0
	Study	99.6	2.85

Table 6. Certainty of evidence

Outcome	Risk of bias	Inconsistency	Indirectness of evidence	Imprecision	Bias of publication	Possible confounder	Certainty
Incidence of postoperative pain 24 hours after endodontic retreatment	-	↓2[a]	-	↓1[b]	-	-	⊕◯◯◯ Very low
Incidence of postoperative pain one week after endodontic retreatment	-	↓2[a]	-	↓1[b]	-	-	⊕◯◯◯ Very low
Intensity of postoperative pain 24 hours after endodontic retreatment	-	↓2[a]	-	↓1[c]	-	-	⊕◯◯◯ Very low

a – No overlap of 95%IC, and tests of heterogeneity with $p < 0.05$ and $I^2 > 75\%$; b – Total of events was less than 300; c – Total of events was less than 400.

meta-analysis, independent of the number of consults, use of solvent(s), solution activation techniques, gutta-percha removal techniques or shape of the automatized file, POP is a common event in 24 hours after retreatment. However, the pain tends to decrease or disappear after one week. In addition, pain intensity did not vary according to the retreatment protocol. These findings present a very low certainty of evidence, and the studies included had an overall low risk of bias.

Amongst the included studies, Yoldas *et al.* [27], Uyan *et al.* [30] and Hepsenoglu *et al.* [9] have evaluated the effect of number of visits on POP; with contradictory results. Hepsenoglu *et al.* [9] has found better prognosis when the retreatment procedure was performed in a single visit. Nevertheless, Yoldas *et al.* [27] and Uyan *et al.* [30] have stated that the use of an antimicrobial intracanal dressing can reduce POP after retreatment. These two authors have justified that the application of an intracanal dressing may probably lower the inflammation of periapical tissues and consequently, help reduce POP. However, none of the mentioned studies used a solvent, and the removal of gutta-percha was carried out with manual files associated with automatized instruments. Pain evaluation was performed using either a pain scale with four defined categories [9, 27] or a 170-mm Heft-Parker visual analogue scale [30]. The difference between the obtained findings could be explained by the subjectivity of their primary outcomes (*i.e.* postoperative pain).

A recent systematic review and meta-analysis has evaluated complications after single-visit or multiple-visit root canal retreatments, and found that both treatment options have presented a similar occurrence of POP [38]. These findings corroborate with a previous systematic review and an overview of published systematic reviews that compared endodontic treatment in single and multiple visits [39, 40]. However, in the current meta-analysis, the number of appointments during NERT in asymptomatic permanent teeth did not change the estimative effect. The incidence and intensity of POP were statistically similar after single-visit and multiple-visit retreatments. Although these findings present a very low certainty of evidence, they are in accordance with the results found in the present systematic review and meta-analysis.

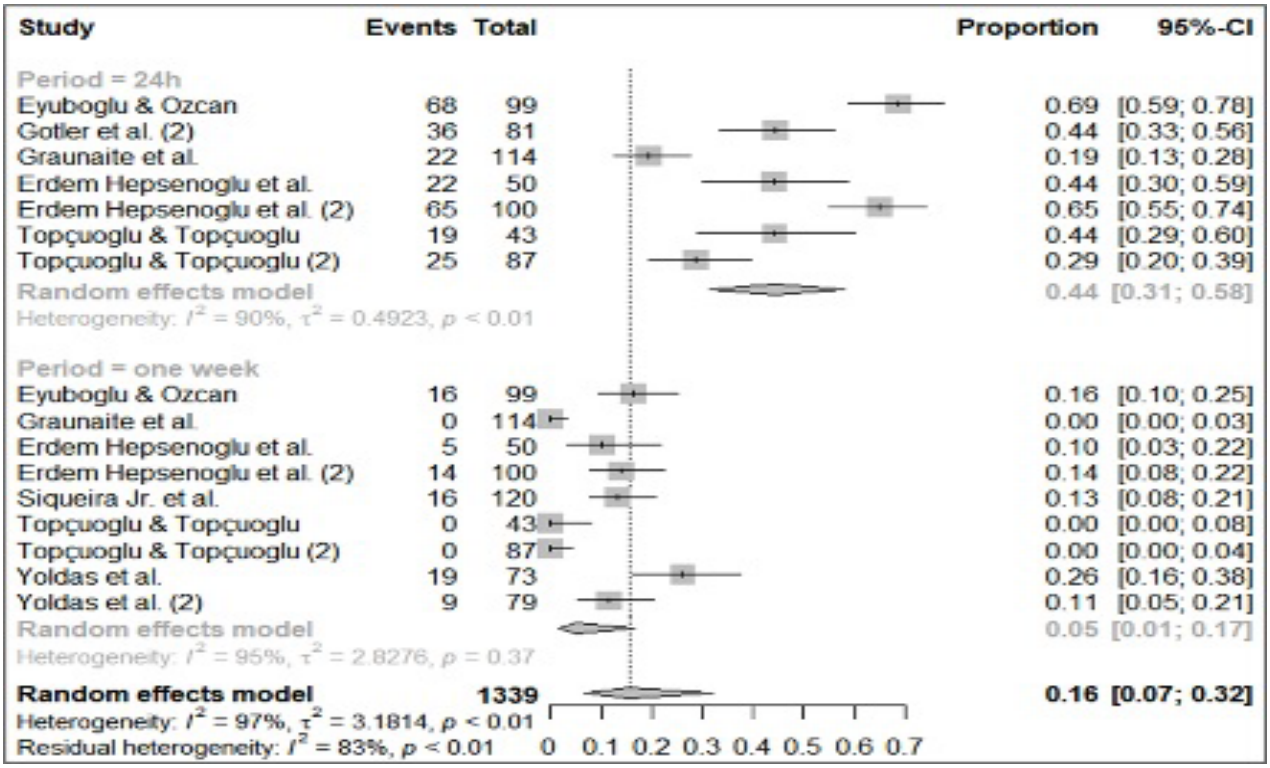

Figure 6. Forest plot diagram for period of analysis of postoperative pain

Solvent was used in six included studies; however, Genc Sen *et al.* [34] only evaluated the effect of usinf or not using solvents on POP after nonsurgical endodontic retreatment. The report has concluded that the use of solvent(s) during NERT has/have not resulted in a significant reduction of POP. This finding corroborates with the results of the present study. Furthermore, the literature has shown that the use of solvent(s) has/have not [41, 42] improved the removal of filling material(s). Campello *et al.* [41] affirm that the use of rotary instruments may make the use of solvents unnecessary for the removal. Therefore, the application of chemical solvents is still recommended to facilitate the removal of gutta-percha via softening of the obturation material in cases of difficult removal with endodontic instruments [43].

The removal technique of gutta-percha has varied immensely amongst studies; nevertheless, Topçuoğlu and Topçuoğlu [29] and Spohr *et al.* [36] have only evaluated the effect of gutta-percha removal technique (manual or automatized) on POP after nonsurgical endodontic retreatment. Topçuoğlu and Topçuoğlu [29] have concluded that the use of hand files can contribute to greater POP only in the first two days after the NERT of upper incisor teeth, compared to the automatized technique. On the other hand, Spohr *et al.* [36] have not detected any difference regarding the prevalence and intensity of POP and analgesic intake after 12 h, 24 h, 48 h and 7 days after each visit for manual or reciprocating techniques. However, they have highlighted that the filling material removal and instrumentation of root canals were more than twice as fast when using the reciprocating system.

Other meta-analyses have found that the use of rotary instruments during endodontic treatment may contribute to lower intensity and incidence of POP compared to the use of hand instruments, and the use of multiple rotary-file systems may lead to lower incidence of pain in comparison to reciprocating instruments [44]. On the other hand, the systematic review published by Martins *et al.* [45] has demonstrated that reciprocating systems may result in less POP compared to the rotary motion. Solda *et al.* [46] have reported that regardless of root canal clearance techniques, debris extrusion eventually occurs during endodontic retreatment and may be related to POP. Keskin and Sarıyılmaz [47] and Li *et al.* [48] have found that rotary and reciprocating systems can cause apical extrusion in cases of retreatment. Delai *et al.* [49] have claimed that a reciprocating system could be associated with less extrusion than hand instruments. Nonetheless, the present meta-analysis found no difference in the incidence and intensity of POP after retreatment, regardless of the technique used.

Furthermore, when just automatized files were evaluated, similar intensity of POP and intake of analgesics following root canal retreatment were found between rotary and reciprocating NiTi instruments [18, 35]. Comparin *et al.* [18] have shown that

both reciprocating and continuous rotary systems are equivalent regarding the incidence, intensity and duration of POP. Comparably, Çanakçi *et al.* [35] have had similar results using 4 different automatized instruments (2 rotary and 2 reciprocating systems). It is worth mentioning that both studies have performed all the retreatments in a single visit. Moreover, some studies have already shown that both continuous rotation and reciprocating motion have displayed similar effectiveness in terms of root canal filling material removal [50]. The only study included, which evaluated a solution activation technique, concluded that EDDY activation resulted in significantly more POP at 12 h, 24 h, 48 h, and 72 h after the procedure than manual dynamic activation. However, the two activation systems showed no differences after 7 days [37]. On the other hand, there are studies showing that EDDY seems to improve debris and smear layer removal compared to manual irrigation [51].

The present meta-analysis showed a statistically significant difference related to the incidence of POP after 24 h and one week following the nonsurgical retreatment procedure. The aforementioned outcome can provide important scientific basis for dental professionals so as to warn the patient on the expected pain as a consequence for NERT beforehand, regardless of the technique used. However, POP tends to be relieved within a week. Previous systematic review evaluating the prevalence and severity of pain during and after endodontic treatment has found that pain severity can drop to minimal levels after 7 days of the root canal treatment when compared to the pain within 24 h after the treatment [52-54].

Prescription of analgesics have been mentioned in a number of studies by Eyuboglu and Özcan [32], Grunaite *et al.* [31], Erdem Hepsenoglu *et al.* [9], Genc Sen *et al.* [34], Genc Sen and Kaya[33], Topçuoğlu and Topçuoğlu [29], Uyan *et al.* [30], Siqueira Jr *et al.* [26], Çanakçi *et al.* [35] in cases with mild or severe pain. However, Yoldas *et al.* [27] and İnce-Yusufoğlu *et al.* [37] have reported that no antibiotics or analgesics needed to be prescribed and Gotler *et al.* [28]and Spohr *et al.* [34] have not stated analgesic prescriptions. Naproxen sodium (500mg), non-steroid analgesics, and ibuprofen (400mg) were the analgesics prescribed for POP. AlRahabi [21] has reported that the adequate management of POP is often considered an indicator of clinical excellence while a flexible, severity-based drug administration plan can be used to control and manage pain after root canal treatment. The studies included in the current systematic review evaluated the POP after NERT. Their primary outcome was the POP, therefore, the use of analgesic. More studies are necessary to evaluate the effect of analgesics on POP and assess the management of POP after endodontic retreatment.

Different methods used in various studies, to assess the intensity of discomfort, have contributed to the exacerbation of heterogeneity between them. Studies are varied in methodologies; involving visual analogue scale (VAS), verbal rating scale (VRS), numeric rating scale (NRS), and scores (no pain, mild pain, moderate pain, and severe pain). The normalization of different scales used in the included studies has enabled their comparison through subgrouping them according to intensity, so that they could be applied in the meta-analysis. The average of POP intensity was converted in a same scale of 0 – 10 mm for all studies; allowing comparison between them. However, the conversion can have a direct effect on the heterogeneity of results; since, although approximate, it will not always accurately reflect the patient's response.

Several etiological factors, e.g. history of preoperative pain, insufficient debridement, premature contact(s), periapical diseases and extrusion of infected debris into the periapical tissues, can contribute to POP [45]. The present systematic review evaluated the effect of NERT and possible related factors on POP. Consequently, studies evaluating patients with preoperative pain were excluded to minimize the effect of painful response on POP. However, the results found in other systematic reviews on endodontic treatment cannot be extrapolated due to the differences between the performed procedures, which are mainly related to the status of the dental pulp and periapical region. In studies on primary endodontic treatment, vital pulp and healthy periapical region are always included at the selected cases. The inflammatory response in these cases can directly affect the incidence and severity of POP; therefore, they cannot be compared with retreatment procedures, when these conditions are usually not presented.

The present systematic review and meta-analysis evaluated the possible factors associated with POP after NERT in permanent and asymptomatic teeth. To standardize the selected articles, the eligibility included clinical studies that evaluated POP after NERT, and excluded articles that evaluated open apex, deciduous teeth and symptomatic cases. Despite the selection, studies showed great heterogeneity regarding the number of visits, use of solvent, removal technique of gutta-percha, pain scale, and period of analysis for POP. Thus, a subgroup division was performed to put similar articles together. Since the conducted analysis were measured after 24 hours and one week in the investigated studies, the two mentioned time periods were chosen for comparisons between the different subgroups at the same time and, eventually, between times.

The current study is the second systematic review and meta-analysis evaluating POP following NERT that has used GRADE approach to reach conclusions through the consideration of the magnitude of effect and certainty of underlying evidence. Nunes *et al.* [38] have evaluated the POP after endodontic retreatment in one single visit against multiple-visit treatments, and have found low levels of evidence due to the inconsistency and imprecision of findings, similar to the present study. However, the very low

certainty of evidence may have been affected by sample size, methodological/clinical heterogeneity, and the subjectivity of pain. More well-designed randomized clinical trials with larger samples, accompanied by controlled methodological and clinical factors; e.g. retreatment protocol, pain scale and sample characteristics, are needed to improve the certainty of evidence.

Conclusion

In accordance with the results found in the current systematic review and meta-analysis, it could be concluded that pain was a common response to nonsurgical endodontic retreatments; independent of the retreatment technique used. The presented findings showed an overall low risk of bias and very low certainty of evidence. To improve the certainty, more well-designed randomized clinical trials, with larger samples, are needed. In the aforementioned trials, patients need to be fully informed of the possible undesired consequences of nonsurgical endodontic retreatments, and the practicing endodontists need to recommend the use of analgesics when necessary. However, the process of pain tends to be relieved within a week.

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