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# Effect of Foraminal Enlargement on Periapical Healing in Necrotic Teeth: A Systematic Review

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**Introduction:** Foraminal Enlargement (FE) is a cleaning performed in the apical-most region of the tooth, in order to optimize root disinfection. This systematic review evaluated the influence of FE during root canal treatment on bacterial reduction and repair of the periapical lesion. **Materials and Methods**: Searches in PubMed/MEDLINE, Scopus, Cochrane Library, Web of Science, Embase, Scielo, Lilacs and OpenGrey were performed until January-2024. *Ex vivo* and *in vivo* studies evaluating the effects of FE in the bacterial reduction and repair of the periapical lesion were included, respectively, followed by risk of bias assessment (modified version of Joanna Briggs Institute's for *ex vivo* studies and Systematic Review Centre for Laboratory animal Experimentation's risk of bias tools for *in vivo* studies). The meta-analysis was not feasible and a qualitative summary for each outcome was provided. **Results**: Of 950 studies, 2 *in vivo* studies were eligible, using animal models with infected teeth. Of these two, periapical repair was evaluated with hematoxylin-eosin stain, and FE improved periapical healing. Regarding *ex vivo* studies, 3 were eligible, using extracted human teeth. The inoculations in *ex vivo* models were performed with *Enterococcus* (*E.*) *faecalis*, and FE reduced *E. faecalis* in the *ex vivo* models. **Conclusions**: Foraminal enlargement seems to increase bacterial reduction within the root canal, and provide major periapical tissue repair on the histological analysis in animal studies. However, caution is necessary when translating these results to the clinical environment.

**Keywords:** Endodontics; Periapical Disease; Periapical Repair; Root Canal Instrumentation; Tissue Healing

## Introduction

Apical periodontitis can cause discomfort for the patient, such as pain and facial swelling [1]. However, despite the high success rate of conventional endodontic treatment, failures can occur due to the persistence of harmful bacterial biofilms within the root canal system [2-4]. To manage the infection and achieve healing of inflamed periradicular tissues, a significant reduction in the number of microorganisms inside the root canal to a level below the threshold that has pathogenic potential, is necessary [4]. In addition to a hermetic filling to prevent the penetration of microorganisms into the root canal system, a satisfactory root canal preparation is also important.

Besides bacterial infection, anatomic complexities might also hinder the capability of clinicians to achieve adequate root disinfection, which negatively affects the desired treatment goals [4-6]. Hence, nonsurgical attempts to treat a tooth with apical periodontitis have been investigated [7, 8]. The determination of the working length and the possibility of performing apical enlargement during root canal preparation may influence the disinfection of the apical-most region of the affected tooth, and therefore, might interfere with the tissue healing process [9-11].

Foraminal enlargement (FE) involves the mechanical instrumentation of the apical foramen, and can be performed by increasing the diameter of instruments in the apical stop when the working length is established in the foramen, or when adopting a working length beyond the apical foramen [12, 13]. This procedure aims to improve the removal of bacteria within the root canal, including the apical foramen area, in which some cases of persistent symptoms have been related to the endurance of extraradicular infection [14].

Although some articles point out the importance of performing FE for microbial reduction [7, 8], this step is not always possible to perform, due to anatomical complications [15]. Additionally, FE has been associated with some concerns, such as the possibility of foraminal deviation and injury to the periapical tissues, indicating that root canal instrumentation should be performed up to apical constriction [16-18]. Regarding this controversial data, this systematic review carried out a search on experimental and animal studies aimed at investigating the influence of FE during root canal preparation on bacterial reduction and repair of periapical lesions in comparison with root canal preparation without FE.

## Materials and Methods

### *Protocol*

This systematic review was carried out in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) [19]. The research protocol was registered at the International Prospective Register of Systematic Review (PROSPERO) database (CRD42022292017).

### *Eligibility criteria*

Inclusion criterion was *in vivo* and/or *ex vivo* studies that evaluated the effects of FE on periapical lesion healing of the root canal system or microbial reduction. The exclusion criteria were: *1*) studies without a control/comparative group and *2*) studies for which the full text was not available. There were no restrictions on the language and publication date.

For the *in vivo* studies, the population, intervention, comparison, and outcome factors (PICO) approach was used to address the following question: "Does FE during endodontic treatment of animal teeth with apical periodontitis influence the healing of periapical lesion and/or the reduce microorganisms compared to root canal preparation without FE?". The study population (P) were animal teeth with apical periodontitis; The intervention (I) was root canal preparation with FE; The comparison (C) was root canal preparation without FE or instrumentation with different diameters of the root foramen; The evaluated outcomes (O) were healing of the periapical lesion and/or reduction in the number of microorganisms within the root canal.

Regarding the *ex vivo* studies, the population, intervention, comparison, and outcome factors (PICO) approach was used to address the following question: "Does FE during endodontic treatment of extracted and infected human teeth influence the reduction of microorganisms compared to root canal preparation without FE?". The study population (P) were extracted human teeth with bacterial inoculation; the intervention (I) was root canal preparation with FE; the comparison (C) was root canal preparation without FE or instrumentation with different diameters of the root foramen; the evaluated outcome (O) was a reduction in the number of microorganisms within the root canal.

### *Search strategy and information sources*

Electronic searches were conducted in the PubMed/MEDLINE, Scopus, Cochrane Library, Web of Science, Embase, Scielo and Lilacs databases up to January-2024. Grey literature was consulted through Google Scholar, and manual searches were also carried out in the reference list of the selected articles. The search strategy used a combination of keywords and Medical Subject Heading terms associated with the Boolean operators "AND" and "OR" and are presented in Table 1.

### *Study selection*

Study selection was carried out independently by three authors (G.O.C.; I.F.A.M. and G.C.F.) in a two-step process. The set of records were organized alphabetically by title so that duplicates could be identified and removed manually. In Step 1, the authors appraised titles and abstracts of the articles retrieved from the search. In Step 2, full text of the remaining studies was obtained for further evaluation. Only studies that fulfilled the eligibility criteria were selected. Disagreements were resolved through discussion and, when necessary, a fourth reviewer (I.C.F.) was consulted. Cohen's kappa coefficient for agreement between investigators during study selection was evaluated [20].

### *Data collection and analyses*

One author (G.O.C.) collected data for all studies using a pilot data extraction form in an Excel spreadsheet. The following data were retrieved: first authors' last name, year of publication, study design, experimental model, sample size, groups, period of observation, and main results of the analyses. Unavailable data were classified as not applicable. Two authors (I.F.A.M. and A.C.D.V) revised the data.

### *Risk of bias assessment*

Two investigators (I.F.A.M. and G.C.F.) independently assessed the selected studies' methodological quality according to their levels of evidence as proposed by a modified version of the Joanna

***Table 1.*** Search strategy used for the electronic databases

| Database | Search Strategy |
|---|---|
| **Medline through PubMed**) | ("apical enlargement"[All Fields] OR "apical preparation"[All Fields] OR "apical expansion"[All Fields] OR "apical widening"[All Fields] OR "foramen widening"[All Fields] OR (("enlarge"[All Fields] OR "enlarged"[All Fields] OR "enlarges"[All Fields] OR "enlarging"[All Fields] OR "enlargment"[All Fields] OR "hypertrophy"[MeSH Terms] OR "hypertrophy"[All Fields] OR "enlargement"[All Fields] OR "enlargements"[All Fields]) AND ("foramen"[All Fields] OR "foramen s"[All Fields] OR "foramens"[All Fields])) OR "foraminal enlargement"[All Fields] OR "foramen enlargement"[All Fields] OR "diameter enlargement"[All Fields] OR "master apical file"[All Fields]) AND ("endodontic treatment"[All Fields] OR "root canal preparation"[All Fields] OR "root canal therapy"[All Fields] OR "endodontic therapy"[All Fields]) AND ("periapical lesion"[All Fields] OR "apical periodontitis"[All Fields] OR (("periapical"[All Fields] OR "periapically"[All Fields] OR "periapicals"[All Fields]) AND "abssess"[All Fields]) OR ("periodontal"[All Fields] OR "periodontally"[All Fields] OR "periodontically"[All Fields] OR "periodontics"[MeSH Terms] OR "periodontics"[All Fields] OR "periodontic"[All Fields] OR "periodontitis"[MeSH Terms] OR "periodontitis"[All Fields] OR "periodontitides"[All Fields]) OR ("perapical"[All Fields] AND ("healed"[All Fields] OR "wound healing"[MeSH Terms] OR ("wound"[All Fields] AND "healing"[All Fields]) OR "wound healing"[All Fields] OR "healing"[All Fields] OR "healings"[All Fields] OR "heals"[All Fields])) OR "periapical tissue healing"[All Fields] OR "periapical healing process"[All Fields] OR "bacterial load"[All Fields] OR "bacterial count"[All Fields] OR "bacterial reduction"[All Fields] OR "bacterial growth"[All Fields] OR "colony-forming units"[All Fields] OR "colony-forming units"[All Fields] OR ("anatomy and histology"[MeSH Subheading] OR ("anatomy"[All Fields] AND "histology"[All Fields]) OR "anatomy and histology"[All Fields] OR "histology"[All Fields] OR "histology"[MeSH Terms] OR "histologies"[All Fields]) OR ("histopathologies"[All Fields] OR "pathology"[MeSH Subheading] OR "pathology"[All Fields] OR "histopathology"[All Fields] OR "pathology"[MeSH Terms]) OR ("histomorphologic"[All Fields] OR "histomorphological"[All Fields] OR "histomorphologically"[All Fields]) OR "histobacteriology"[All Fields] OR ("radiograph"[All Fields] OR "radiographed"[All Fields] OR "radiographer"[All Fields] OR "radiographer s"[All Fields] OR "radiographers"[All Fields] OR "radiographic"[All Fields] OR "radiographical"[All Fields] OR "radiographically"[All Fields] OR "radiographics"[All Fields] OR "radiographing"[All Fields] OR "radiographs"[All Fields]) OR ("radiography"[MeSH Terms] OR "radiography"[All Fields] OR "diagnostic x ray"[All Fields]) OR "diagnostic x ray"[All Fields] OR ("tomographie"[All Fields] OR "tomography"[MeSH Terms] OR "tomography"[All Fields] OR "tomographies"[All Fields] OR "tomography s"[All Fields] OR "tomography, x ray computed"[MeSH Terms] OR ("tomography"[All Fields] AND "x ray"[All Fields] AND "computed"[All Fields]) OR "x-ray computed tomography"[All Fields] OR "tomographys"[All Fields])) |
| **Scopus** | TITLE-ABS-KEY (("apical enlargement" OR "apical preparation" OR "apical expansion" OR "apical widening" OR "foramen widening" OR "enlargement foramen" OR "foraminal enlargement" OR "foramen enlargement" OR "diameter enlargement" OR "master apical file") AND ("endodontic treatment" OR "root canal preparation" OR "root canal therapy" OR "endodontic therapy") AND ("periapical lesion" OR "apical periodontitis" OR "periapical bssess" OR periodontitides OR "perapical healing" OR "periapical tissue healing" OR "periapical healing process" OR "bacterial load" OR "bacterial count" OR "bacterial reduction" OR "bacterial growth" OR "colony forming units" OR "colony-forming units" OR histology OR histopathology OR histomorphologic OR histobacteriology OR radiographic OR diagnostic AND x-ray OR "diagnostic x ray" OR tomography)) |
| **Cochrane** | (("apical enlargement" OR "apical preparation" OR "apical expansion" OR "apical widening" OR "foramen widening" OR "enlargement foramen" OR "foraminal enlargement" OR "foramen enlargement" OR "diameter enlargement" OR "master apical file") AND ("endodontic treatment" OR "root canal preparation" OR "root canal therapy" OR "endodontic therapy") AND ("periapical lesion" OR "apical periodontitis" OR "periapical abssess" OR periodontitides OR "perapical healing" OR "periapical tissue healing" OR "periapical healing process" OR "bacterial load" OR "bacterial count" OR "bacterial reduction" OR "bacterial growth" OR "colony forming units" OR "colony-forming units" OR histology OR histopathology OR histomorphologic OR histobacteriology OR radiographic OR diagnostic x-ray OR "diagnostic x ray" OR tomography)):ti,ab,kw |
| **Web of Science** | ALL=(("apical enlargement" OR "apical preparation" OR "apical expansion" OR "apical widening" OR "foramen widening" OR "enlargement foramen" OR "foraminal enlargement" OR "foramen enlargement" OR "diameter enlargement" OR "master apical file") AND ("endodontic treatment" OR "root canal preparation" OR "root canal therapy" OR "endodontic therapy") AND ("periapical lesion" OR "apical periodontitis" OR "periapical abssess" OR periodontitidis OR "perapical healing" OR "periapical tissue healing" OR "periapical healing process" OR "bacterial load" OR "bacterial count" OR "bacterial reduction" OR "bacterial growth" OR "colony forming units" OR "colony-forming units" OR histology OR histopathology OR histomorphologic OR histobacteriologic OR radiographic OR diagnostic x-ray OR "diagnostic x ray" OR tomography)) |
| **Embase** | ('apical enlargement' OR 'apical preparation' OR 'apical expansion' OR 'apical widening' OR 'foramen widening' OR 'enlargement foramen' OR 'foraminal enlargement' OR 'foramen enlargement' OR 'diameter enlargement' OR 'master apical file') AND ('endodontic treatment' OR 'root canal preparation'/exp OR 'root canal preparation' OR 'root canal therapy'/exp OR 'root canal therapy' OR 'endodontic therapy') AND ('periapical lesion'/exp OR 'periapical lesion' OR 'apical periodontitis'/exp OR 'apical periodontitis' OR 'periapical abssess' OR periodontitides OR 'perapical healing' OR 'periapical tissue healing' OR 'periapical healing process' OR 'bacterial load'/exp OR 'bacterial load' OR 'bacterial count'/exp OR 'bacterial count' OR 'bacterial reduction' OR 'bacterial growth'/exp OR 'bacterial growth' OR' colony forming units' OR 'colony-forming units' OR 'histology'/exp OR histology OR 'histopathology'/exp OR histopathology OR histomorphologic OR histobacteriology OR radiographic OR 'diagnostic x-ray' OR (('diagnostic'/exp OR diagnostic) AND ('x ray'/exp OR 'x ray')) OR 'diagnostic x ray' OR 'tomography'/exp OR tomography) |
| **Scielo** | ("apical enlargement" OR "apical preparation" OR "apical expansion" OR "apical widening" OR "foramen widening" OR "enlargement foramen" OR "foraminal enlargement" OR "foramen enlargement" OR "diameter enlargement" OR "master apical file") AND ("endodontic treatment" OR "root canal preparation" OR "root canal therapy" OR "endodontic therapy") AND ("periapical lesion" OR "apical periodontitis" OR "periapical abssess" OR periodontitides OR "perapical healing" OR "periapical tissue healing" OR "periapical healing process" OR "bacterial load" OR "bacterial count" OR "bacterial reduction" OR "bacterial growth" OR "colony forming units" OR "colony-forming units" OR histology OR histopathology OR histomorphologic OR histobacteriology OR radiographic OR diagnostic x-ray OR "diagnostic x ray" OR tomography) |
| **Lilacs** | (("apical enlargement" OR "apical preparation" OR "apical expansion" OR "apical widening" OR "foramen widening" OR "enlargement foramen" OR "foraminal enlargement" OR "foramen enlargement" OR "diameter enlargement" OR "master apical file") AND ("endodontic treatment" OR "root canal preparation" OR "root canal therapy" OR "endodontic therapy") AND ("periapical lesion" OR "apical periodontitis" OR "periapical abssess" OR periodontitides OR "perapical healing" OR "periapical tissue healing" OR "periapical healing process" OR "bacterial load" OR "bacterial count" OR "bacterial reduction" OR "bacterial growth" OR "colony forming units" OR "colony-forming units" OR histology OR histopathology OR histomorphologic OR histobacteriology OR radiographic OR diagnostic x-ray OR "diagnostic x ray" OR tomography)) |
| **Google Scholar** | ("foramen widening" OR "foraminal enlargement" OR "foramen enlargement") AND ("endodontic" OR "root canal therapy") AND ("periapical lesion" OR "apical periodontitis" OR "periapical healing" OR "bacterial load" OR "bacterial reduction" OR histology) |

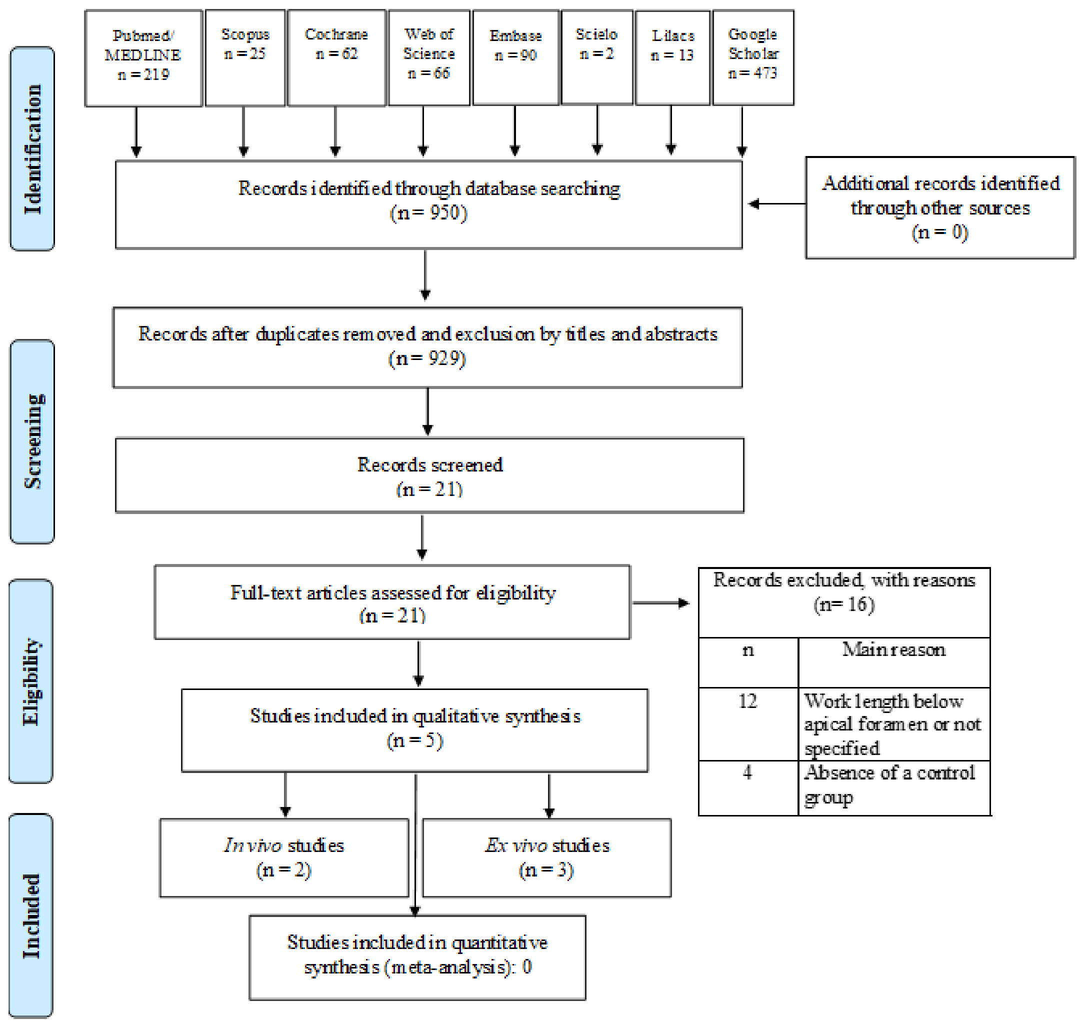


***Figure 1.*** Flow diagram of the search strategy of the systematic review following the PRISMA guidelines

Briggs Institute's Critical Evaluation Checklist for Experimental Studies [21, 22]. The assessed items were as follows: clearly stated aim, sample size justification (the authors either described the sample size and power calculation methods or justified the sample size used in the study), sample randomization, blind treatment allocation, possibility of comparison between control and treatment groups, baseline equivalence of control and treatment groups, measurement standardization, reliable measurement method, and appropriate statistical analysis. Each item was assessed on a 2-point scale: 0, not reported or reported inappropriately, and 1, reported and appropriate. The 10-criteria tool of Systematic Review Centre for Laboratory animal Experimentation (SYRCLE's risk of bias tool) was used to assess the risk of bias of the animal studies [23]. The assessed domains were: adequate generation of allocation sequence, similarity of groups at baseline or adjustment of confounder due to differences between groups, adequate allocation concealment, random housing, blinded intervention/outcome assessment, sample randomization for outcome assessment, incomplete outcome data, selective outcome reporting, presence of other biases, and sample size justification to further characterize reporting in the selected animal studies. A judgment of "no" indicated a high risk of bias, "yes" represented a low risk of bias, and "unclear" indicated either uncertainty or lack of information. Discrepancies were resolved with a third examiner (G.O.C.).

## Results

### *Search results*

The selection process of the articles is presented in Figure 1. A total of 950 articles were screened. After the initial screening, 21 articles were selected for full-text evaluation that resulted in the exclusion of 16 articles with reasons shown in Figure 1. Lastly, two *in vivo* articles met the inclusion criteria and were included in the qualitative analysis [7, 8], along with three *ex vivo* studies [24-26]. No additional articles were found through manual search in the reference lists.

The assessed Cohen's kappa coefficient value for inter-investigator agreement was equal to 0.870 for PubMed, 1.000 for Scopus, 1.000 for the Cochrane Library, 0.882 for Web of Science, 0.860 for Embase, 1.000 for Scielo, 1.000 for Lilacs, and 1.000 for Google Scholar. These values indicated an almost perfect agreement among reviewers according to the scale of Landis & Koch, 1977 [20].

***Characteristics of the included studies***

*In vivo*

Data regarding the characteristics of the studies are described in Table 1. No in vivo human studies comparing endodontic treatment with and without FE were identified. However, two eligible studies [7, 8] involving animals (rats and dogs) were included, where the teeth were deliberately opened for a certain period of time to induce infection. The sample size ranged from 10 to 12 teeth per group.

In both studies, the control group underwent instrumentation 1 mm below the apical foramen, while the experimental group received instrumentation up to the foramen. Mechanized endodontic instruments were not used; instead, manual instruments were employed in both groups, with both using a 2.5% sodium hypochlorite (NaOCl) solution. The evaluation periods were 4 weeks [8] and 180 days [7].

The periapical lesion was induced in the animals' teeth after the access preparation of these teeth and being left open for three weeks [8] and 180 days [7]. Once periapical lesions were induced, tissue repair was evaluated after four weeks [8] and 180 days [7] through histological analysis using hematoxylin and eosin staining [7, 8]. In both studies, FE promoted better periapical healing with cementum neoformation and a reduction in the number of inflammatory cells compared to the group without FE.

Radiographic evaluation was performed in one study [8], which demonstrated a greater regression of the periapical lesion in the group with FE.

*Ex vivo*

Table 2 presents information about the three included studies [24-26]. The *ex vivo* models involved extracted human teeth, including molars, premolars and canines [24-26] with *E. faecalis* inoculation. Among these articles, most of them had a sample size ranging from 3 to 15 teeth per group.

Regarding the used working lengths, all studies had a control group with instrumentation 1 mm below the apical foramen. In the experimental groups, one article's sample groups received instrumentation up to apical foramen [24], whereas the other two had a group with instrumentation level reaching 1 mm beyond the apical foramen [25, 26]. In these studies, root canal preparation was performed by hand instrumentation with K-files [24] or mechanized instrumentation with rotary or reciprocating nickel-titanium files [25, 26], such as Reciproc R50 [26], Protaper Next [25] and WaveOne Gold [25]. For root canal disinfection, 2.5% NaOCl [25, 26] and 17% ethylenediaminetetraacetic acid were mostly used [24-26]; however, 5.25% NaOCl [24], 0.9% sodium chloride [25] and saline solution [24, 26] were also reported. Regarding the observation periods, the studies reported an immediate evaluation.

Table 1 summarizes the results of the evaluated outcomes in each selected study from this systematic review. Data are described below.

Colony-forming unit was used for bacterial analysis in all *ex vivo* studies [24-26], and *E. faecalis* was chosen for inoculation. Observation periods of 72 h or 21 days were reported. Among all these studies, FE group increased bacterial reduction in root canals in comparison to the instrumentation performed 1 mm below the root foramen.

***Synthesis of results***

Due to variations among studies, mainly in study methodology, bacterial inoculation time and evaluation methods, meta-analysis was not performed. A qualitative summary was provided instead.

***Risk of bias assessment within ex vivo and animal studies***

Critical appraisal of the included studies is presented in Figure 2. To assess the risk of bias in *ex vivo* studies, the Joanna Briggs Institute's tool was used (Figure 2A). All records showed a clearly stated aim, possibility of comparison between the control and treatment groups at entry, baseline equivalence among the groups, measurement standardization, and reliable outcome assessment. Low risk of bias was also observed in the appropriate statistical approach. However, a high risk of bias was found only for specific items, such as justification of sample size, sample randomization and blinded outcome assessment. Figure 2B summarize the risk of bias of animal studies by using the SYRCLE tool. Information to judge most evaluated domains was absent mainly in adequate generation of allocation sequence, adequate allocation concealment, random housing, blinded intervention, and sample size justification. A low risk was observed in the remaining evaluated items.

***Table 2.*** Characteristics of the studies included in the systematic review

| Author | Study design | Experimental model | n | Groups | Analysis period | Bacterial analysis | Histological analysis | Radiographic analysis |
|---|---|---|---|---|---|---|---|---|
| Brandão *et al.* [8] | *In vivo* | Mesial canals of rat lower first molars left open, 3 weeks | 10-12 | #15 to #30 K-files; 2.5% NaOCl; Sterile saline; Single cone technique and AH-Plus; G1 and G2: no treatment; G3: WL up to the AF; G4: 1 mm short of the AF | 4 weeks after treatment | N.A. | HE; G1 and G2: > inflammation and < cementum neoformation than G3 and G4; G3: = inflammation and > cementum neoformation than G4 | Area of periapical radiolucency, mm; G1: 1.452 ±0.446 #; G2: 1.699 ±0.224 #; G3: 0.801 ±0.458 =; G4: 1.373 ±0.269 # |
| Borlina *et al.* [7] | *In vivo* | Dogs teeth open, 180 days | 10 | #55 K-file, G1 and G2 #25 up to AF; 2.5% NaOCl; 17% EDTA; $Ca(OH)_2$; Lateral condensation; G1: WL up to the AF, Sealer 26; G2: Endomethasone; G3: without foramen widening, Sealer 26; G4: Endomethasone | 180 days after treatment | N.A. | HE; G1 and G2: > cementum neoformation, repair of areas of cementum, periapical healing process, periodontal ligament condiditons and < bone resorption, presence of microorganisms and inflammatory cell infiltrate than G3 and G4 | N.A. |
| Yadav *et al.* [24] | *Ex vivo* | Human maxillary molars infected with *E. faecalis*, 72 h | 5-8 | K-files; 5.25% NaOCL; 17% EDTA; Phosphate-buffered normal saline. G1: no treatment; G2: WL up to the AF #25; G3: 1 mm short of the AF | Immediate | CFU; G1: >$10^5$ #; G2: 350=; G3 9.000 § | N.A. | N.A. |
| Sacomani *et al.* [26] | *Ex vivo* | Human canines infected with *E. faecalis*, 21 days | 5-15 (Control =5 and Experimental group =15) | Reciproc R50; 2.5 NaOCl, 17% EDTA, 0.9% Saline solution; G1: no treatment; G2: without bacterial inoculation; G3: WL -1 mm to the AF; G4: WL up to the AF; G5: WL +1 mm to the AF | Immediate | CFU, $10^5$; G1: 18.214 ±8.868; G2: 0; G3: 0.86 ±1.28 #; G4: 0.27 ±0.25 #=; G5: 0.18 ±0.28 = | N.A. | N.A. |
| Lins *et al.* [25] | *Ex vivo* | Human premolars infected with *E. faecalis*, nm | 3-5 (Control = 3 and Experimental group = 5) | 17% EDTA with activation; G1: no treatment; G2: no treatment with bacterial inoculation; G3: WL -1 mm, PTN, 2.5% NaOCl; G4: WL 0 mm, PTN, 2.5% NaOCl; G5: WL +1 mm, PTN, 2.5% NaOCl; G6: WL -1 mm, WOG, 2.5% NaOCl; G7: WL 0 mm, WOG, 2.5% NaOCl; G8: WL +1 mm, WOG, 2.5% NaOCl; G9: WL -1 mm, PTN, 0.9% NaCl; G10: WL 0 mm, PTN, 0.9% NaCl; G11: WL +1 mm, PTN, 0.9% NaCl; G12: WL -1 mm, WOG, 0.9% NaCl; G13: WL 0 mm, WOG, 0.9% NaCl; WL +1 mm, WOG, 0.9% NaCl | Immediate | CFU, $10^5$; G1: 0 #; G2: >$10^5$ =; G3, G4, G6, G7 and G8: 0 #; G5, G9-G14: >$10^5$ = | N.A. | N.A. |

*WL: Working Length; AF: Apical Foramen; FE: Foraminal enlargement; nm: not mentioned; NaOCl: sodium hypochlorite; h: hours; d: days; w: weeks; EDTA: Ethylenediamine tetraacetic acid; CaOH2: Calcium hydroxide; PTN: Protaper Next; WOG: WaveOne Gold; NaCl: Sodium chloride; NA: Not Applicable; HE: Hematoxylin-eosin; CFU: Colony-forming units; #=§+ Different letters indicate statistically significant difference*

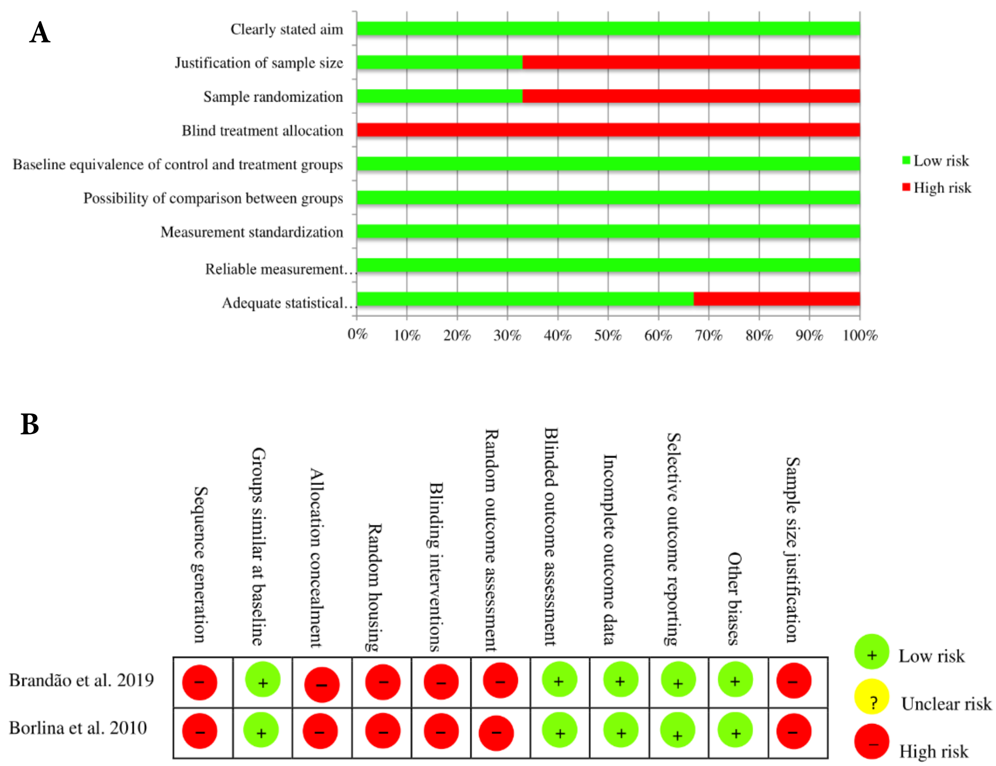


***Figure 2.*** Assessment of the risk of bias in the included studies; *A) Ex vivo* studies risk of bias, using Joanna Briggs Institute's tool; *B)* animal studies risk of bias, using SYRCLE tool

## Discussion

The present systematic review evaluated whether FE influences the reduction of microorganisms and healing of periapical lesion compared to root canal treatment without FE. Data from five *in vivo* and *ex vivo* studies were included for these evaluations [7, 8, 24-26]. Based on the design and results of the studies incorporated in this review, FE emerges as a promising approach to enhance root canal system disinfection, fostering increased bacterial reduction and improving periapical repair compared to instrumentation without FE.

The presence of bacterial biofilms is related to the maintenance and progression of the periapical lesion [27, 28]. However, due to anatomical complexity, infection control becomes challenging [29-31]. Foraminal enlargement with intentional instrumentation beyond or up to the apical foramen is an alternative for bacterial control [24-26]. Enlarging the foramen in teeth with periapical lesions has been proposed in order to optimize the disinfection in the area next to the periapical tissues, and prevent possible bacteria proliferation in this critical region. Therefore, the removal of microorganisms in this region may favor periapical repair, due to the reduced inflammatory reaction after a decrease in microbial factors disseminated into the apical tissue [32-34]. Despite the possible benefits of FE, there are also some concerns, such as the formation of dentinal microcracks in the apical region [35], foramen deviation [12] and postoperative pain after root canal treatment [1]. Additionally, FE may increase the amount of apically extruded debris and irrigants to the periapical area [36]. Therefore, careful preparation of root canal with FE is necessary for clinicians in order to avoid the dissemination of debris and solutions into the periapical area [37, 38].

In this systematic review, bacterial reduction was evaluated in the included studies using extracted human teeth inoculated with *E. faecalis* [24-26]. Root canal preparation with instrumentation up to the foramen or beyond resulted in a greater removal of bacteria inside the root canals immediately after instrumentation of the teeth in the selected studies. However, Sacomani *et al.* [26] demonstrated a correlation in intragroup reduction, regardless of the adopted working length (1 mm short, up to the apex, or 1 mm beyond), with all groups showing a significant reduction in the quantity of *E. faecalis*. Nevertheless, only a few studies were found in the literature search, which demonstrates the need for more research on this outcome, mainly in vivo studies, in order to simulate the clinical setting and consider anatomical complexity and bacterial diversity of endodontic microbiota. These evaluations may increase the reliability of evidence regarding the effects of FE in microbial reduction within the root canal system.

Regarding periapical tissue healing, studies using animal models have evaluated tissue repair in teeth with induced periapical lesion after four weeks [8] and 180 days [7] of intervention. Periapical tissue healing represents an important long-term outcome of endodontic treatment. A well-performed endodontic treatment allows the organism to repair periapical tissues, leading to bone neoformation and periodontal ligament repair [2, 3]. The included studies showed that FE might improve periapical tissue healing with a significant reduction in the number of inflammatory cells in the area. This result can be associated with the decrease in the amounts of microorganisms and endotoxins during apical preparation, which can lead to tissue repair in the region through the reduction of pro-inflammatory cytokines, and the formation of a mineralized tissue [39]. Similarly, Jara *et al.* [33] compared the effect of FE with three different diameters of instruments in rat molars, and concluded that instrumentation with larger instrument diameters provides a faster radiographic repair of the periapical lesion. Therefore, a greater microbial reduction after preparation with larger apical enlargement can be strongly associated to a better periapical healing [40].

A radiographic evaluation also showed a considerable regression of the lesion when FE was performed [8]. However, radiographic image does not exactly match the histological environment, and the size of the radiographic lesion does not coincide with the actual size of the lesion in the histopathological or tomographic view [41]. It is important to emphasize that the irrigating protocols used in the included studies may also have an impact on the outcome. For instance, all the studies used 2.5% [7, 8, 25, 26] and 5.25% [24] NaOCl as the irrigating solution, which can enhance bacterial reduction, and consequently, improve periapical healing [11, 42]. Furthermore, an evaluation of periapical lesion reduction through the analysis of tomographic images is also necessary due to a greater sensitivity of this method and the possibility of a three-dimensional evaluation in comparison to conventional radiography, which might underestimate the size of the periapical lesion [41].

Regarding the critical appraisal of the included articles, the selected *ex vivo* studies [24-26] have a low-risk of bias, which suggests an overall reliable evidence. However, methodological issues were observed, especially regarding blind evaluation, since it is an important step to avoid biased results for any of the groups. Blinding is a step present in this study model and needs to be improved in future researches. In the animal studies [7, 8] certain biases were observed, mainly involving the randomization of animals during the experiment and evaluation, the allocation sequence and the justification of the sample size, which suggests that some caution must be exercised in the interpretation of the study results. Operator blinding is complicated to perform, since the steps vary in relation to the technique. Further histological analyses using animal models with high reporting quality are encouraged in order to minimize biases and avoid exaggerated effects.

On the basis of this review, we noticed a small number of *ex vivo* studies and histological evaluation in animal models assessing the effects of FE on bacterial reduction and periapical tissue repair, respectively. Most of the studies evaluate the impact of root canal instrumentation up to the apical foramen or 1 mm beyond, without a comparison group with no foraminal preparation [16, 43, 44], which points out the need for future well-designed pre-clinical studies comparing different working length determinations on the assessed outcomes for stronger evidence. Furthermore, an evaluation using teeth with curved canals are necessary, following the pattern of commonly observed anatomy. Nevertheless, findings of laboratory studies should be carefully analyzed before being clinically considered. Regarding bacterial reduction, higher-level evidence is required; and for periapical healing, additional clinical animal studies are necessary. Performing FE causes discomfort for the patient, especially in the first days after receiving the treatment [1]. Therefore, randomized clinical studies that compare the long-term success rates of endodontic treatments that consider patient-based endodontic outcomes with FE are encouraged.

## Conclusion

Within the limitations of this systematic review, *in vivo* studies suggest FE enhances tissue repair, while *ex vivo* studies suggest a notable increase in bacterial reduction within the root canal associated with FE. However, caution is necessary when translating these results to the clinical environment.

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None.

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***Authors' contributions***

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## References


1. Borges Silva EA, Guimarães LS, Küchler EC, Antunes LAA, Antunes LS. Evaluation of Effect of Foraminal Enlargement of Necrotic Teeth on Postoperative Symptoms: A Systematic Review and Meta-analysis. J Endod. 2017;43(12):1969-77.
2. Siqueira JF, Jr., Rôças IN. Clinical implications and microbiology of bacterial persistence after treatment procedures. J Endod. 2008;34(11):1291-301.e3.
3. Ricucci D, Siqueira JF, Jr. Biofilms and apical periodontitis: study of prevalence and association with clinical and histopathologic findings. J Endod. 2010;36(8):1277-88.
4. Siqueira JF, Jr., Rôças IN. Present status and future directions: Microbiology of endodontic infections. Int Endod J. 2022;55 Suppl 3:512-30.
5. Ricucci D, Siqueira JF, Jr. Anatomic and microbiologic challenges to achieving success with endodontic treatment: a case report. J Endod. 2008;34(10):1249-54.
6. Khan MT, Moeen F, Safi SZ, Said F, Mansoor A, Khan A. The Structural, Physical, and In Vitro Biological Performance of Freshly Mixed and Set Endodontic Sealers. Eur Endod J. 2021;6(1):98-109.
7. Borlina SC, de Souza V, Holland R, Murata SS, Gomes-Filho JE, Dezan Junior E, Marion JJ, Neto Ddos A. Influence of apical foramen widening and sealer on the healing of chronic periapical lesions induced in dogs' teeth. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2010;109(6):932-40.
8. Brandão PM, de Figueiredo JAP, Morgental RD, Scarparo RK, Hartmann RC, Waltrick SBG, Souza RA. Influence of foraminal enlargement on the healing of periapical lesions in rat molars. Clin Oral Investig. 2019;23(4):1985-91.
9. Estrela C, Holland R, Estrela CR, Alencar AH, Sousa-Neto MD, Pécora JD. Characterization of successful root canal treatment. Braz Dent J. 2014;25(1):3-11.
10. Sant'Anna Júnior A, Cavenago BC, Ordinola-Zapata R, De-Deus G, Bramante CM, Duarte MA. The effect of larger apical preparations in the danger zone of lower molars prepared using the Mtwo and Reciproc systems. J Endod. 2014;40(11):1855-9.
11. Holland R, Gomes JEF, Cintra LTA, Queiroz Í OA, Estrela C. Factors affecting the periapical healing process of endodontically treated teeth. J Appl Oral Sci. 2017;25(5):465-76.
12. Silva Santos AM, Portela F, Coelho MS, Fontana CE, De Martin AS. Foraminal Deformation after Foraminal Enlargement with Rotary and Reciprocating Kinematics: A Scanning Electronic Microscopy Study. J Endod. 2018;44(1):145-8.
13. Machado R, Vigarani G, Macoppi T, Pawar A, Glaci Reinke SM, Kovalik Gonçalves AC. Extrusion of debris with and without intentional foraminal enlargement - A systematic review and meta-analysis. Aust Endod J. 2021;47(3):741-8.
14. Ricucci D, Siqueira JF, Jr., Lopes WS, Vieira AR, Rôças IN. Extraradicular infection as the cause of persistent symptoms: a case series. J Endod. 2015;41(2):265-73.
15. Souza RA, Sousa YT, de Figueiredo JA, Dantas Jda C, Colombo S, Pécora JD. Influence of apical foramen lateral opening and file size on cemental canal instrumentation. Braz Dent J. 2012;23(2):122-6.
16. de Souza Filho FJ, Benatti O, de Almeida OP. Influence of the enlargement of the apical foramen in periapical repair of contaminated teeth of dog. Oral Surg Oral Med Oral Pathol. 1987;64(4):480-4.
17. Ricucci D. Apical limit of root canal instrumentation and obturation, part 1. Literature review. Int Endod J. 1998;31(6):384-93.
18. Machado R, Ferrari CH, Back E, Comparin D, Tomazinho LF, Vansan LP. The impact of apical patency in the success of endodontic treatment of necrotic teeth with apical periodontitis: a brief review. Iran Endod J. 2016;11(1):63-6..
19. Page MJ, Moher D, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, Shamseer L, Tetzlaff JM, Akl EA, Brennan SE, Chou R, Glanville J, Grimshaw JM, Hróbjartsson A, Lalu MM, Li T, Loder EW, Mayo-Wilson E, McDonald S, McGuinness LA, Stewart LA, Thomas J, Tricco AC, Welch VA, Whiting P, McKenzie JE. PRISMA 2020 explanation and elaboration: updated guidance and exemplars for reporting systematic reviews. BMJ. 2021;372:n160.
20. Landis JR, Koch GG. The measurement of observer agreement for categorical data. Biometrics. 1977;33(1):159-74.
21. Yaylali IE, Kececi AD, Ureyen Kaya B. Ultrasonically Activated Irrigation to Remove Calcium Hydroxide from Apical Third of Human Root Canal System: A Systematic Review of In Vitro Studies. J Endod. 2015;41(10):1589-99.
22. Dos Reis-Prado AH, Abreu LG, Tavares WLF, Peixoto I, Viana ACD, de Oliveira EMC, Bastos JV, Ribeiro-Sobrinho AP, Benetti F. Comparison between immediate and delayed post space preparations: a systematic review and meta-analysis. Clin Oral Investig. 2021;25(2):417-40.
23. Hooijmans CR, Rovers MM, de Vries RB, Leenaars M, Ritskes-Hoitinga M, Langendam MW. SYRCLE's risk of bias tool for animal studies. BMC Med Res Methodol. 2014;14:43.
24. Yadav SS, Shah N, Naseem A, Roy TS, Sood S. Effect of "apical clearing" and "apical foramen widening" on apical ramifications and bacterial load in root canals. Bull Tokyo Dent Coll. 2014;55(2):67-75.

25. Lins RP, Araújo RPCd, Silva SJAd, Reis JNJRdOdU. Análise da desinfecção apical do canal radicular preparado em três diferentes comprimentos de trabalho, utilizando movimento rotatório contínuo ou reciprocante e duas substâncias irrigadoras: estudo in vitro. 2019;48:e20190002.
26. Sacomani AC, Cintra FT, de Jesus Soares A, Frozoni MJR, Society, Development. The influence of working length on the reduction of biofilm and planktonic bacteria in oval canals with reciprocating instrumentation. 2021;10(5):e9810514765-e.
27. Mickel AK, Chogle S, Liddle J, Huffaker K, Jones JJ. The role of apical size determination and enlargement in the reduction of intracanal bacteria. J Endod. 2007;33(1):21-3.
28. Bronzato JD, Bomfim RA, Hayasida GZP, Cúri M, Estrela C, Paster BJ, Gomes B. Analysis of microorganisms in periapical lesions: A systematic review and meta-analysis. Arch Oral Biol. 2021;124:105055.
29. Yammine S, Jabbour E, Nahas P, Majzoub Z. Foramen changes following over instrumentation of curved canals with three engine-driven instruments: an in vitro study. Iran Endod J. 2017;12(4):454-61.
30. Siqueira Junior JF, Rôças IDN, Marceliano-Alves MF, Pérez AR, Ricucci D. Unprepared root canal surface areas: causes, clinical implications, and therapeutic strategies. Braz Oral Res. 2018;32(suppl 1):e65.
31. Wolf TG, Stiebritz M, Boemke N, Elsayed I, Paqué F, Wierichs RJ, Briseño-Marroquín B. 3-dimensional Analysis and Literature Review of the Root Canal Morphology and Physiological Foramen Geometry of 125 Mandibular Incisors by Means of Micro-Computed Tomography in a German Population. J Endod. 2020;46(2):184-91.
32. Card SJ, Sigurdsson A, Orstavik D, Trope M. The effectiveness of increased apical enlargement in reducing intracanal bacteria. J Endod. 2002;28(11):779-83.
33. Jara CM, Hartmann RC, Böttcher DE, Souza TS, Gomes MS, Figueiredo JAP. Influence of apical enlargement on the repair of apical periodontitis in rats. Int Endod J. 2018;51(11):1261-70.
34. Fatima S, Kumar A, Andrabi S, Mishra SK, Tewari RK. Effect of Apical Third Enlargement to Different Preparation Sizes and Tapers on Postoperative Pain and Outcome of Primary Endodontic Treatment: A Prospective Randomized Clinical Trial. J Endod. 2021;47(9):1345-51.
35. Jamleh A, Nassar M, Alfadley A, Khan S, Alfouzan K, Adorno C. Influence of additional apical enlargement on microcrack formation in root dentine: a micro-computed tomography investigation. Clin Oral Investig. 2021;25(6):4137-43.
36. Guivarc'h M, Ordioni U, Ahmed HM, Cohen S, Catherine JH, Bukiet F. Sodium Hypochlorite Accident: A Systematic Review. J Endod. 2017;43(1):16-24.
37. Albuquerque PP, Hungaro Duarte MA, Pelegrine RA, Kato AS, Stringheta CP, Duque JA, Bueno C. Influence of foraminal enlargement on the apical extrusion of filling material: Volumetric analysis using micro-computed tomography. Aust Endod J. 2020;46(2):210-6.
38. de Freitas Portela FSM, De Martin AS, Pelegrine RA, Gutmann JL, Kato AS, Bueno C. Effect of Foraminal Enlargement on Postoperative Pain in Necrotic Single-Rooted Teeth: A Randomized Clinical Trial. J Endod. 2021;47(7):1046-51.
39. Salles AG, Antunes LAA, Küchler EC, Antunes LS. Association between Apical Periodontitis and Interleukin Gene Polymorphisms: A Systematic Review and Meta-analysis. J Endod. 2018;44(3):355-62.
40. Rodrigues RCV, Zandi H, Kristoffersen AK, Enersen M, Mdala I, Ørstavik D, Rôças IN, Siqueira JF, Jr. Influence of the Apical Preparation Size and the Irrigant Type on Bacterial Reduction in Root Canal-treated Teeth with Apical Periodontitis. J Endod. 2017;43(7):1058-63.
41. Leonardi Dutra K, Haas L, Porporatti AL, Flores-Mir C, Nascimento Santos J, Mezzomo LA, Corrêa M, De Luca Canto G. Diagnostic Accuracy of Cone-beam Computed Tomography and Conventional Radiography on Apical Periodontitis: A Systematic Review and Meta-analysis. J Endod. 2016;42(3):356-64.
42. Soares JA, Pires Júnior DR. Influence of sodium hypochlorite-based irrigants on the susceptibility of intracanal microbiota to biomechanical preparation. Braz Dent J. 2006;17(4):310-6.
43. Rollison S, Barnett F, Stevens RH. Efficacy of bacterial removal from instrumented root canals in vitro related to instrumentation technique and size. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2002;94(3):366-71.
44. Mohammadzadeh Akhlaghi N, Rahimifard N, Moshari A, Vatanpour M, Darmiani S. The Effect of Size and Taper of Apical Preparation in Reducing Intra-Canal Bacteria: A Quantitative SEM Study. Iran Endod J. 2014;9(1):61-5.

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