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The influence of periodontal attachment loss on the outcome of endodontic microsurgery: a systematic review and meta-analysis

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ABBREVIATIONS LIST

AP – Apical periodontitis

BP-RRM – Bioceramic paste root repair material

CRR - Crown-to-root ratio

DOI – Digital object identifyer

EMS – Endodontic microsurgery

IRM – Zinc oxide-eugenol intermediate restorative cement

ME – Microcirurgia endodôntica

MTA – Mineral trioxide aggregate

NSER - Nonsurgical endodontic retreatment

PRISMA - Preferred reporting items for systematic reviews and meta-analyses

RCT – Randomized controlled trial

RoB2 – Risk of bias 2

ROBINS-I – Risk of bias in non-randomised studies

SER - Surgical endodontic retreatment

SuperEBA – Super ethoxybenzoic acid

ABSTRACT

Introduction: Endodontic microsurgery (EMS) aims to eradicate the sources of infection once the apical root resection removes most of the infected anatomical structures and repairs procedural errors in the apical third of the root. Periodontitis is defined as chronic multifactorial inflammatory disease triggered by dysbiotic bacterial microorganisms that gradually promote the destruction of the supporting structures of the tooth, with a high prevalence among the adult population. An endodontic-periodontal lesion is defined by a pathological communication between the pulp and the periodontium.

Objective: The purpose of this systematic review and meta-analysis is to evaluate the influence of periodontal attachment loss on the outcome of teeth submitted to endodontic microsurgery.

Materials and Methods: This systematic review and meta-analysis followed the PRISMA guidelines. An electronic search was performed in EBSCOhost, Embase and PubMed databases with the following search ("endodontic microsurgery" AND outcome). No filters were used concerning the year of publication. Only randomized clinical trials, prospective and retrospective clinical studies in humans, with a minimum follow-up of 1-year, clinical and radiographic criteria and success rate for endodontic-periodontal lesion, were included. Statistical analysis was performed by "OpenMeta [Analyst]" software.

Results: Of a total of 113 articles, 34 were selected for full-text reading after the exclusion of duplicates and title and abstract reading. Of these articles, 13 were included in the systematic review and only 6 of these studies were included in the meta-analysis. The studies included in this review included 2775 teeth subjected to EMS of which 492 teeth and 4 roots had periodontal involvement. Of the studies included in the qualitative analysis, the success rates for the endo-perio group ranged from 67,6% to 88,2%. The meta-analysis showed that absence of periodontal attachment loss was predictive of a higher likelihood of success with an Odds Ratio of 3,14.

Conclusion: This systematic review and meta-analysis concluded that periodontal attachment loss is a risk factor for the outcome for the EMS. However, EMS performed in endodontic-periodontal lesions is a fully valid and viable procedure in teeth with this type of lesion, allowing relatively high long-term success rates as revealed by the longer follow-up periods of the studies included. Future clinical studies should be conducted to evaluate the influence of the tooth type, single- or multi-rooted teeth, as well as the occlusal relationships in teeth with periodontal attachment loss on the prognosis of EMS.

Keywords: endodontic microsurgery; apicoectomy; endodontic-periodontal lesion; isolated endodontic lesion; prognostic factors; outcome

RESUMO

Introdução: A microcirurgia endodôntica (ME) visa erradicar as fontes de infeção, uma vez que a resseção apical da raiz remove a maioria das estruturas anatómicas infetadas e repara erros que possam ocorrer no terço apical da raiz. A periodontite é uma doença inflamatória crónica multifatorial desencadeada por microrganismos bacterianos disbióticos que, gradualmente, promovem a destruição das estruturas de suporte do dente e apresenta uma elevada prevalência na população adulta. Uma lesão endodôntico-periodontal ocorre quando existe uma comunicação patológica entre a polpa e o periodonto.

Objetivo: O objetivo desta revisão sistemática e meta-análise é avaliar a influência da perda de suporte periodontal no prognóstico de dentes submetidos a microcirurgia endodôntica.

Materiais e Métodos: Esta revisão sistemática e meta-análise seguiu as diretrizes PRISMA. Foi realizada uma pesquisa eletrónica nas bases de dados EBSCOhost, Embase e PubMed com a seguinte pesquisa: ("endodontic microsurgery" AND outcome). Não foram utilizados filtros relativos ao ano de publicação. Apenas foram incluídos ensaios clínicos randomizados e estudos clínicos prospetivos e retrospetivos em humanos, com um "follow-up" mínimo de 1 ano, critérios clínicos e radiográficos e taxa de sucesso para lesão endodôntico-periodontal. A análise estatística foi realizada através do software "OpenMeta [Analyst]".

Resultados: De um total de 113 artigos obtidos, 34 foram selecionados para leitura integral após a exclusão de duplicados e leitura de título e resumo. Destes artigos, 13 foram incluídos na revisão sistemática e, apenas 6 foram incluídos na meta-análise. Os estudos incluídos nesta revisão incluíram 2775 dentes submetidos a ME, dos quais 492 dentes e 4 raízes tinham um envolvimento periodontal. Dos estudos incluídos na análise qualitativa, as taxas de sucesso para o grupo endo-perio variaram entre os 67,6% e os 88,2%. A meta-análise demonstrou que a ausência de perda de suporte periodontal foi preditiva de uma maior probabilidade de sucesso com um Odds Ratio de 3,14.

Conclusão: Esta revisão sistemática e meta-análise concluiu que a perda de suporte periodontal é um fator de risco para o prognóstico da ME. Contudo, a ME em lesões endodônticas-periodontais é um procedimento totalmente válido e viável em dentes com este tipo de lesão, permitindo taxas de sucesso relativamente elevadas a longo prazo, conforme revelado pelos "follow-ups" mais longos dos estudos incluídos. Estudos clínicos futuros devem ser conduzidos no sentido de avaliar a influência do tipo de dente, mono ou multirradiculares, bem como as relações oclusais em dentes com perda de suporte periodontal no prognóstico do EMS.

Palavras-chave: microcirurgia endodôntica; apicectomia; lesão endodôntica periodontal; lesão endodôntica isolada; fatores de prognóstico; prognóstico

INTRODUCTION

The main objective of endodontic treatment is to prevent or cure apical periodontitis (AP), caused by infection of the root canal systems, due to the exposure of the vital pulp to different oral microorganisms, which leads to necrosis of the dental pulp and the development of infection in the periapical region of the affected teeth. Thus, the host's immune response is activated resulting in local inflammation, resorption and destruction of periapical tissues, and formation of periapical lesions [1,2].

Several studies suggest that 33 to 60% of root-filled teeth present AP, due to the primary infection or emergence of a secondary infection [1,3]. Jakovljevic *et al.* show an increase in worldwide prevalence of AP in the general adult population, especially among people over 50 years old, which can be explained by the high prevalence of dental caries, traumatic accidents or other iatrogenic causes due to the increasing demand for conservative treatments [2].

The main causes for root canal treatment failure are extraradicular infection, foreign body reaction, persistent infection in the root canal system caused by complex anatomical structures at the periradicular area and periradicular cysts. However, several iatrogenic factors may be related to post treatment endodontic disease, such as root perforation, ledge formation, instrument fracture and overfilling [4,5].

Nonsurgical endodontic retreatment (NSER) remains the desirable treatment option to manage apical periodontitis, avoiding tooth extraction and dental implant placement, allowing the preservation of the natural tooth [1,6]. Nevertheless, surgical endodontic retreatment (SER) is also indicated to eradicate persistent apical periodontitis, as a last resort treatment when nonsurgical retreatment is considered not feasible, impractical, or unlikely to improve the previous condition [5,7–12].

Endodontic microsurgery (EMS) aims to eradicate the sources of infection once the apical root resection removes most of the infected anatomical structures and repairs procedural errors in the apical third of the root [4,11]. EMS also provides a hermetic seal of the root canal system, enabling healing as it forms a barrier between the affected root and the surrounding tissues, achieved by root-end preparation and the following obturation [11,13].

Endodontic microsurgery is a surgical procedure characterized by the use of an operating microscope that improves illumination and magnification, root-end preparation with ultrasonic devices, and root-end filling with biocompatible materials [7,14]. The microscope is essential to identify the most minute details of the apical anatomy and to examine the resected root surface in order to identify and correct the cause of failure of the previous treatment [6,7,14]. The ultrasonic instruments assist the root-end preparation within the anatomic space of the canal [15,16].

These surgical advances allow endodontic surgical procedures to be executed with precision and predictability, eliminating difficulties associated with traditional endodontic surgery as poor visualization, inaccurate root-end preparation, and large osteotomy [15–17]. After the introduction of this "modern techniques", the success rate of EMS increased from 59% to 94% [18].

Most studies on EMS show high success and survival rates which reveal that this procedure is very efficient. However, these studies have very specific and restrictive inclusion criteria which may jeopardize their external validity to regular practice settings. Therefore, their results may not reflect the effectiveness of interventions in real-life routine conditions, in general population [11,14,15,19].

Periodontitis is defined as chronic multifactorial inflammatory disease triggered by dysbiotic bacterial microorganisms that gradually promote the destruction of the supporting structures of the tooth, such as the alveolar bone and the periodontal ligament. Periodontal attachment loss is diagnosed by the presence of periodontal pocket, gingival bleeding, clinical attachment loss and radiographic evidence of alveolar bone loss [20].

The recent Global Burden of Disease Study reveals that severe periodontitis is the sixth most prevalent disease worldwide, with a prevalence of 11.2% and over 743 million people affected. This form of periodontal disease has an enormous impact on the quality of life of the affected individuals, as it may lead to tooth loss, affecting considerably the masticatory function [20–22].

Periodontitis is associated with several chronic inflammatory systemic diseases. Currently, there is an aging population as well as an increasing need for health care. Consequently, periodontitis will continue to rise as the growing aging of the population leads to increased tooth retention, which means that people preserve more teeth for longer and with increasingly severe periodontal pathology, with bone loss [21,22].

An endodontic-periodontal lesion occurs when there is a pathological communication between the pulp and the periodontal tissue [20,23]. Regarding EMS in such clinical diagnosis, two scenarios may occur: the tooth subjected to the procedure may be posteriorly affected by periodontal attachment loss accompanied by surrounding alveolar bone loss, or a tooth already affected by periodontal disease could undergo EMS [24].

In either scenario, EMS decreases root length, altering the crown-to-root ratio (CRR), as well as remaining periodontal support. This procedure modifies the biomechanical response of the tooth, causing unfavourable stress distribution and increased tooth mobility, which may influence tooth function and survival as the tooth remains exposed to continuous occlusal loading [4,25].

However, periodontal bone loss also aggravates CRR, simultaneously increasing the length of the clinical crown and decreasing the length of the supported root. Periodontal bone loss has a greater influence on biomechanical parameters than the apical root resection itself, once most of the stress from occlusal loading is concentrated on the cervical third of the root, not on the apical third [4,24,25].

The patient's occlusion also has a great impact in the tooth stability after EMS. In all occlusal relationships, the stress and tooth displacement maximum values at the cervix, root apex, alveolar bone and periodontal ligament increased as the resection length increased [4].

Thus, it is possible to find numerous studies on the prognosis of EMS, but few include teeth with periodontal pathology associated. Periodontally involved teeth are believed to have an adverse impact on the outcome of EMS [7]. As a result, most studies evaluating potential prognostic factors related to the outcome of endodontic microsurgery exclude teeth with probing depths > 4 mm or apico-marginal root damage (fracture or cracking, canal or chamber perforation, external root resorption) [7,19].

Kim and Kratchman proposed a classification of lesion types in endodontic surgical cases, into categories A-F [12]. This classification includes teeth periodontally involved and for that reason is the most accepted classification defining the degree of periodontal involvement in teeth subjected to EMS. This classification is entirely described in Supplementary Table 1.

Considering the high prevalence of periodontal disease nowadays, the probability of occurrence of a case with apical periodontitis in a tooth with periodontal involvement needing to resort to an endodontic microsurgery procedure is quite high. For that reason and due to the lack of evidence in the literature for this kind of situations, it is extremely important to clarify the effect of periodontal attachment loss on the outcome of this surgical procedure. Thus, the purpose of this systematic review and meta-analysis is to evaluate the influence of periodontal attachment loss on the outcome of teeth submitted to endodontic microsurgery.

MATERIALS AND METHODS

Prior to literature search, a research question was defined according to the paradigm of evidence-based dentistry, following the PEO (Population, Exposure and Outcome) systematic review of risk protocol suggested by Joanna Briggs Institute:

1. Population: teeth with periodontal attachment loss.

2. Exposure: endodontic microsurgery.

3. Outcome: clinical and radiographic success of the endodontic microsurgery.

This review aimed to answer the following questions: “Are teeth with periodontal attachment loss submitted to endodontic microsurgery at higher risk of failure? Do they have poorer clinically and radiographically outcome?”

Searching criteria

The selection of studies for this systematic review was based on the following inclusion and exclusion criteria:

Inclusion criteria

1. Clinical studies in humans.
2. Randomized clinical trials (RCT) in endodontic microsurgery.
3. Prospective clinical studies in endodontic microsurgery.
4. Retrospective clinical studies in endodontic microsurgery.
5. Teeth indicated for endodontic microsurgery (periapical lesion, secondary apical periodontitis, extrusion of root canal filling material resulting from primary endodontic treatment, persistent extra-radicular infection).
6. Studies in which the procedure was described with precision or sustained the modern technique using magnification devices (microscope and endoscope) and ultrasonic root-end preparation.
7. Clinical and radiographic criteria and success rate estimable.
8. A minimum follow-up period of 1 year.
9. Periodontal attachment loss quantified.

Exclusion criteria

1. Studies that included patients aged under 18-years.
2. Studies that excluded teeth with periodontal attachment loss.
3. Systematic review.
4. Case series.
5. Case report.
6. The procedure was not described with precision or did not sustain the modern technique.
7. Follow-up inferior to 1 year.

8. Absence of periodontal attachment loss quantification.
9. Studies in which radiographic and clinical success criteria and success rate for endodontic-periodontal lesion were not estimable.

Searching method

An initial search, limited to the Journal of Endodontics was conducted to gather topic-related studies, regardless of the publication type. The information collected from the analysis of those studies helped to develop a search strategy, including identifying the keywords and index terms to perform the actual search for this systematic review.

Afterwards, three electronic databases were used: EBSCOhost, Embase and PubMed.

The search terms were (“endodontic microsurgery” AND outcome), for each database.

In addition, this search was supplemented by hand search checking references of the most relevant articles found in the initial search.

Study selection

The study selection ended in April 2021. All the obtained articles were individually scanned by two reviewers (MS, JMS). First of all, duplicates were identified and removed. Secondly, two researchers (MS, JMS) independently screened the title and abstract of each article identified in the search in order to establish its eligibility, excluding those which did not meet the main subject. Then, the included studies were subject to a full-text evaluation to identify those who did meet the inclusion criteria previously defined. If any disagreement on study inclusion or exclusion occurred during the selection process, a third examiner (IPB) was consulted.

Data extraction

Two authors (MS, JMS) participated independently in the data extraction process. General information about each article that met eligibility criteria was collected to create a table of evidence.

An Excel table was constructed containing the following topics: identification of the study (title, authors and DOI), year of publication, study design, sample size, diagnostic criteria of periodontal attachment loss, tooth type, root filling material, follow-up period, recall rate, success rates for both lesion type groups (isolated endodontic and endo-perio lesions), measure unit, type of anaesthesia, additional haemostasis strategies and regeneration materials.

Quality assessment

The methodological quality evaluation of the eligible studies was conducted prior to inclusion in this review. These assessments were performed independently by two authors (JMS, MS). Two Cochrane risk-of-bias assessment tools (RoB2 and ROBINS-I) were applied as well as the Newcastle-

Ottawa Scale. The randomized controlled trial was assessed by the RoB2 tool and both prospective and retrospective cohort studies utilized the ROBINS-I tool and the Newcastle-Ottawa Scale.

Meta-analysis

The pertinent data from the studies included in the qualitative analysis were extracted and presented in Table 1. Descriptive analysis was used to identify similarities and variations between the studies. Only the studies that followed the Kim and Kratchman classification [12] as diagnostic criteria of periodontal attachment loss were considered for meta-analysis.

Studies were pooled in a statistical meta-analysis of proportions with difference of arcsines transformation using "OpenMeta [Analyst]" software. Heterogeneity was assessed statistically using the the standard Chi-square and I^2 tests. Statistical analyses were then performed using DerSimonian-Laird binary random-effects at a confidence interval of 95%.

RESULTS

Study selection

The flowchart according to PRISMA guidelines is provided in Figure 1.

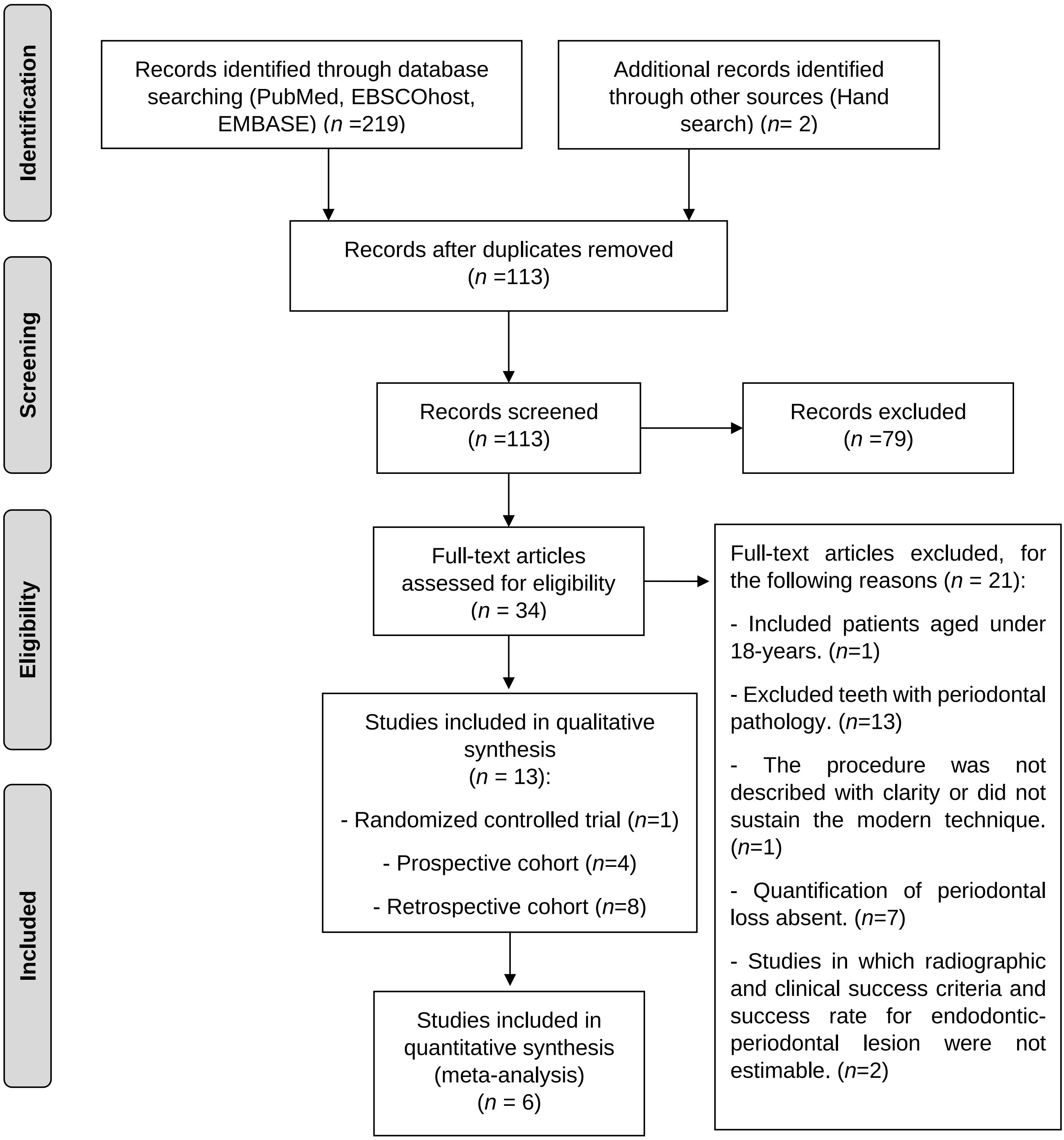

Figure 1. Flowchart of article selection method according to The PRISMA Statement.

A total of 219 articles were obtained in the electronic search, and 2 articles were identified from the hand search. After eliminating de duplicates, 113 articles remained. The titles and abstracts of the 113 selected articles were screened and 79 articles were excluded. Then, the remaining 34 articles were subjected to full-text analysis to assess for eligibility, and 21 were excluded [26–46] according to the reasons listed in Supplementary Table 2. Finally, 13 articles were chosen to be included in the qualitative assessment: 1 randomized controlled trial [8], 4 prospective cohort studies [13–15,47] and 8 retrospective cohort studies [9–11,17,19,48–50]. For the quantitative assessment, only 6 articles were included: 2 prospective cohort studies [14,15] and 4 retrospective cohort studies [9,11,19,50].

Study Characteristics

Table 1 presents the detailed data concerning the studies included in this review.

Of a total of 2775 teeth subjected to EMS, 492 teeth and 4 roots had periodontal involvement. All studies included anterior teeth, premolars, and molars, although none specified the distribution of the tooth type of the endo-perio group.

The diagnostic criteria of endo-perio lesions differ between the studies: some resorted to the classification proposed by Kim and Kratchman [9,11,14,15,19,50], others used the criteria of marginal bone loss or probing depth above 3 millimetres [10,13,47–49], alveolar dehiscence [8] and periodontal involvement [17].

Regarding the retrofilling material, the majority of the studies preferred zinc oxide-eugenol intermediate restorative material (IRM) [9–11,14,15,19,48], mineral trioxide aggregate (ProRootMTA) [8–11,13–15,17,19,47–50] and super ethoxy-benzoic acid (SuperEBA) [9,11,13–15,19,47,49].

The tooth was always considered as the unit of evaluation, except for one study, which the root was assessed as a single unit [48].

The anaesthetic protocol included mostly 2% lidocaine and 1:80000 epinephrine. However, two studies used 2% lidocaine and 1:100000 epinephrine [8,17] and other two 4% articaine and 1:100000 epinephrine [13,49]. For additional haemostasis, epinephrine, ferric sulphate or aluminium chloride were used in some cases [9,10,13–15,17,19,47–50].

The follow-up period ranged from 1 year [8,11,13,19] to a maximum follow-up of 10 years [9,14]. The maximum recall rate was 100% in two studies [11,50] and the minimum was 34,5% [17].

Concerning the endo-perio group, the higher success rate was 95,7% [9] and the lowest was 33,3% [17]. However, the validity of these outcomes is undermined by the sample size [17,48] and by the fact that Song et al. [9] has been considered an outlier. Therefore, the success rates for the endo-perio group ranged from 67,6% to 88,2% [8,10,11,13–15,19,47,49,50]. Most studies had a success rate of the endo group higher than the endo-perio group, disregarding two studies, which demonstrates that teeth periodontally involved had better success rates than those not affected [9,13].

Finally, six studies applied collagen resorbable membranes and/ or bone substitutes for guided bone regeneration procedures [8–10,15,17,48].

Study	Study design	Sample size (teeth)			Diagnostic criteria of periodontal attachment loss	Root filling material	Follow up period	Recall rate	Success rate		Regeneration	
		n initial	*n* final	*n* endo-perio					Endo-group	Endo-perio group	Y/N	Material
Zhou et al 2017 [8]	Randomized Controlled Trial	240	158	17	Alveolar dehiscence	ProRoot MTA BP-RRM	1 year	65,8%	94,3%	88,2%	Y	collagen resorbable membrane
von Arx et al 2007 [13]	Prospective cohort	194	191	43	Marginal bone level >3 mm	Super EBA ProRoot MTA Retroplast	1 year	98,5%	83,1%	86,1%	N	
Kim E et al 2008 [15]	Prospective cohort	263	192	40	Kim and Kratchman	IRM Super EBA ProRoot MTA	2 years	73%	95,3%	77,5%	Y	calcium sulfate + collagen resorbable membrane (CollaTape)
Song et al 2013 [47]	Prospective cohort	199	135	33	Marginal bone loss >3 mm	Super EBA ProRoot MTA	1-7 years	67,8%	89,3%	87,9%	N	
Song et al 2013 [14]	Prospective cohort	584	431	87	Kim and Kratchman	IRM Super EBA ProRoot MTA	1-10 years	73,8%	88,4%	74,7%	N	
Song et al 2011 [19]	Retrospective cohort	907	491	50	Kim and Kratchman	IRM, Super EBA, ProRoot MTA	At least 1 year	54,1%	84,8%	70%	N	
von Arx et al 2012 [49]	Retrospective cohort	194	170	37	Crestal bone level >3mm	Super EBA ProRoot MTA Retroplast	5 years	87,6%	78,2%	67,6%	N	
Song et al 2012 [9]	Retrospective cohort	172	104	23	Kim and Kratchman	IRM Super EBA ProRoot MTA	6-10 years	60,5%	92,6%	95,7%	Y	collagen resorbable membrane (CollaTape)

Table 1. Summary of the included studies in the systematic review. Bioceramic paste root repair material (BP-RRM), zinc oxide-eugenol intermediate restorative cement (IRM), mineral trioxide aggregate (MTA), Super ethoxybenzoic acid (SuperEBA), dentine-bonded resin composite (Retroplast), hydraulic calcium zirconia complex (RetroMTA), MTA-derived pozzolan cement (Endocom MTA), yes (Y), no (N), resorbable collagen membrane (CollaTape), bone substitute (BioOss). * Specifically in this study the measure unit refers to root.

Study	Study design	Sample size (teeth)			Diagnostic criteria of periodontal attachment loss	Root filling material	Follow up period	Recall rate	Success rate		Regeneration	
		***n* initial**	***n* final**	***n* endo-perio**					**Endo-group**	**Endo-perio group**	**Y/N**	**Material**
Lui et al 2014 [10]	Retrospective cohort	243	93	14	PD>3 mm	IRM MTA	1-2 years	38%	95,2%	73%	Y	collagen resorbable membrane (BioMend) and bone substitute (BioOss)
Song et al 2018 [11]	Retrospective cohort	249	249	83	Kim and Kratchman	IRM, Super EBA, ProRoot MTA	1 year	100%	87,3%	72,3%	N	
Kim D et al 2020 [50]	Retrospective cohort	244	244	56	Kim and Kratchman	SCSM group (gray or white ProRootMTA) FCSM group (RetroMTA or Endocem MTA)	1-6 years	100%	94,7%	71,4%	N	
Huang et al 2020 [48]	Retrospective cohort	191	92 95*	4*	Preoperative periodontal probing length >3mm	IRM ProRoot MTA	5-9 years	48,2%	80,8%	50%	Y	collagen resorbable membrane
Yoo et al 2020 [17]	Retrospective cohort	652	225	9	Periodontal involvement	ProRoot MTA	5 years	34,5%	82,4%	33,3%	Y	BioOss

Quality Assessment

This systematic review included only a randomized controlled trial [8], which quality assessment, applying the Cochrane Rob 2 tool (Table 2) identified the final risk of bias as 'low'. The twelve remaining prospective and retrospective cohort studies were assessed by the Newcastle–Ottawa Scale (Table 3), two studies [17,48] scored seven stars and the other ten studies [9–11,13–15,19,47,49,50] scored eight stars out of a maximum of nine stars. The same twelve studies were assessed by the Cochrane ROBINS-I tool (Table 4), and the risk of bias was assessed as 'low' for seven [9,11,13–15,48–50], 'moderate' for two [19,47] and 'high' for three [10,17,48].

	D1	D2	D3	D4	D5	
Study	**Randomization process**	**Deviations from the intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported result**	**Overall risk of bias**
Zhou et al 2017 [8]	LOW	LOW	LOW	LOW	LOW	LOW

Table 2. Risk-of-bias in randomized controlled trials based on the RoB2 tool, as recommended by Cochrane.

Studies	Selection	Comparability	Outcome	Overall merit
von Arx et al 2007 [13]	★★★★	★	★★★	8 stars
Kim E et al 2008 [15]	★★★★	★	★★★	8 stars
Song et al 2013 [47]	★★★★	★	★★★	8 stars
Song et al 2013 [14]	★★★★	★	★★★	8 stars
Song et al 2011 [19]	★★★★	★	★★★	8 stars
von Arx et al 2012 [49]	★★★★	★	★★★	8 stars
Song et al 2012 [9]	★★★★	★	★★★	8 stars
Lui et al 2014 [10]	★★★★	★	★★★	8 stars
Song et al 2018 [11]	★★★★	★	★★★	8 stars
Kim D et al 2020 [50]	★★★★	★	★★★	8 stars
Huang et al 2020 [48]	a)★★★	★	★★★	7 stars
Yoo et al 2020 [17]	b)★★★	★	★★★	7 stars

Table 3. Risk-of-bias in cohort studies based on the Newcastle-Ottawa Scale. a) The exposed cohort was not representative because there were only 4 roots with periodontal involvement in a total sample of 95 roots. b) The exposed cohort was not representative because there were only 9 teeth with periodontal involvement in a total sample of 225 teeth.

	D1	D2	D3	D4	D5	D6	D7	
Study	**Bias due to Confounding**	**Bias in Selecting Participants for the Study**	**Bias in Classifying Interventions**	**Bias due to Deviations from Intended Intervention**	**Bias due to Missing Data**	**Bias in Measuring Outcomes**	**Bias in Selecting Reported Result**	**Overall judgement**
von Arx et al 2007 [13]	LOW	LOW	LOW	LOW	LOW	MODERATE[c)]	LOW	LOW
Kim E et al 2008 [15]	LOW	LOW	LOW	LOW	LOW	LOW	LOW	LOW
Song et al 2013 [47]	LOW	LOW	LOW	LOW	MODERATE[a)]	MODERATE[c)]	LOW	MODERATE
Song et al 2013 [14]	LOW	LOW	LOW	LOW	LOW	MODERATE[c)]	LOW	LOW
Song et al 2011 [19]	LOW	LOW	LOW	LOW	MODERATE[a)]	MODERATE[c)]	LOW	MODERATE
von Arx et al 2012 [49]	LOW	LOW	LOW	LOW	LOW	LOW	LOW	LOW
Song et al 2012 [9]	LOW	LOW	LOW	LOW	MODERATE[a)]	LOW	LOW	LOW
Lui et al 2014 [10]	LOW	LOW	LOW	LOW	HIGH[b)]	LOW	LOW	HIGH
Song et al 2018 [8]	LOW	LOW	LOW	LOW	LOW	MODERATE[c)]	LOW	LOW
Kim D et al. 2020 [50]	LOW	LOW	LOW	LOW	LOW	MODERATE[c)]	LOW	LOW
Huang et al 2020 [48]	LOW	LOW	LOW	LOW	HIGH[b)]	LOW	LOW	HIGH
Yoo et al 2020 [17]	LOW	LOW	LOW	LOW	HIGH[b)]	MODERATE[c)]	LOW	HIGH

Table 4. Risk-of-bias in cohort studies based on the ROBINS-I tool, as proposed by Cochrane. a) Recall rate between 50 and 70%. b) Recall rate less than 50%. c)The outcome assessors were not blind to the intervention received by study participants.

Meta-analysis

The meta-analysis showed a clear tendency to favour the endo group, as only one study [9] evaluated presented higher success rates for the endo-perio group than the endo group. From the pooled teeth, the overall showed that absence of periodontal attachment loss was predictive of a higher likelihood of success with an Odds Ratio of 3,14 (95% confidence interval: 2,023 to 4,87) as shown in Figure 2.

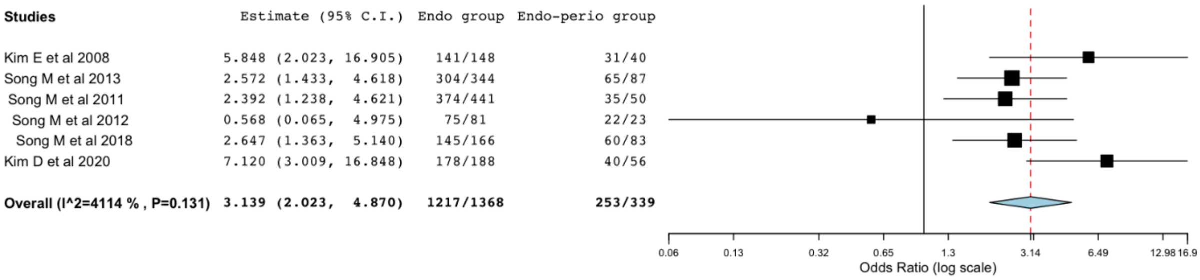

Figure 2. Forest plot of Odds Ratio of success in the endo group compared to the endo-perio group. Confidence Interval (CI).

DISCUSSION

Apical periodontitis, caused by the infection of the root canal systems [1], has a high prevalence among the general adult population [2,3]. In fact, when nonsurgical retreatment is insufficient or not feasible to allow the preservation of teeth with persistent apical periodontitis, a surgical approach is essential [8]. The EMS aims to eliminate the entire necrotic tissue from the surgical site, to provide a hermetic seal of the root canal system and enable the restauration of the integrity of hard and soft tissues, allowing the reestablishment of the dentogingival complex [15].

Regarding the follow-up period, surgical retreatment cases are prone to heal faster than nonsurgical ones [51]. Song *et al.* [9] demonstrated that the most relevant evidence concerning the healing process was obtained at the first-year post-surgery and that the variation in the clinical outcome between the follow-up period of 1 year and 4 or more years was not significant. Hence, the 1-year follow-up may be sufficient to predict long-term outcome of EMS [8]. Therefore, the present systematic review established a minimum follow-up period of 1 year for study inclusion, resulting in studies ranging from 1 to 10 years of follow-up.

The effect of the root-end filling material is one of the most studied outcome factors of EMS, among the intraoperative factors. EMS requires more biocompatible materials, such as IRM, Super EBA, MTA, Retroplast among others [19]. MTA is the preferred root-end filling material in EMS, in most of the studies included in this systematic review [10,13,15,19,48,49]. MTA has the ability to stimulate bone, dentin, and cementum formation, promoting tissue regeneration, such as the periodontal ligament and cementum [15]. Von Arx *et al.* [49] also suggested that the most effective seal over a follow-up period of 5 years was achieved with MTA. However, Zhou *et al.* [8] found no significant difference in the clinical outcomes of EMS between MTA and BP-RRM, both showed favourable biocompatibility, no cytotoxic effects and similar sealing performance. However, one of the studies [14] found no significant influence in success rate, regarding the root-end filling material. The other 3 studies [11,17,47] did not evaluate the effect of the root-end filling material on the outcome of EMS.

Periodontitis is responsible for alveolar bone and periodontal ligament loss, and apical migration of epithelial root adhesion, which may jeopardize the healing process after EMS. Therefore, the prognosis of periodontally involved teeth relies on both periodontal support and endodontic microsurgery [9,17,19]. Owing to that fact, endodontic-periodontal lesions are known as one of the most challenging scenarios in the SER field [24]. A tooth may have independent or communicating endodontic and periodontal lesions. Whereas a lesion may also be initially endodontic or periodontal with a subsequent involvement of one another [24]. When a pathological communication occurs between the pulp and periodontal tissues through the apex, lateral canals, and dentinal tubules, an endodontic-periodontal combined lesion arises [52].

EMS is considered a high success procedure, although it usually covers endodontic lesions without any periodontal complications [15], once endodontic-periodontal lesions are believed to have a worse prognosis than isolated endodontic lesions [11,53]. However, as mentioned previously in this review, in real clinical situations many cases include some degree of periodontal involvement [15]. Therefore, the lesion type seems to be a significant predictor of outcome [14,19,50].

Song *et al.* [14] reported weighty predictors of success for endodontic-periodontal combined lesions, such as age, sex, tooth position, arch type, and lesion type.

Concerning the tooth type, the impact of periodontal pathology in the EMS prognosis is believed to differ between a single and a multi-rooted tooth. Periodontal bone loss aggravates the CRR, decreasing the length of the supported root simultaneously increasing the length of the clinical crown [4,24,25].

In a single-rooted tooth, periodontal bone loss has a greater influence on biomechanical parameters than the apical root resection itself. Stress from occlusal loading is mostly concentrated at the cervical third of the root, not at the apical third [4,24,25].

In a multi-rooted tooth, the bone loss at the apical level will not affect the prognosis as unfavourably as if it occurred at the cervical level, once the volume at the cervical level that the tooth occupies is more significant than at the apical portion. However, none of the studies included in this systematic review specified the distribution of the tooth type of the group with periodontal involvement and, for that reason, it is not possible to draw conclusions about the possible influence of the tooth type, mono- or multirooted with periodontal attachment loss on the prognosis of EMS. Thus, future clinical studies should be conducted to evaluate the influence of the type of tooth, single- or multi-rooted teeth, with periodontal attachment loss on the prognosis of endodontic microsurgery.

The patient's occlusion also has a great impact in the tooth stability after EMS. In all occlusal relationships, the stress and tooth displacement maximum values at the cervix, root apex, alveolar bone and periodontal ligament increased as the resection length increased [4]. The prognosis of EMS may differ between the various occlusal relationships. Ran *et al.* shows that the stress and tooth displacement maximum values were the greatest with increased overjet, followed by normal occlusions and increased overjet with deep overbites. Deep overbites had the lowest values [4].

As for lesion type, Lui *et al.* [10] evaluated the influence of alveolar dehiscence on the outcome of EMS and considered that the existence or not of buccal bone dehiscence may not constitute a prognostic factor. Von Arx *et al.* [54] studied the effect of bone defects size on the healing outcome of EMS, and also found that the marginal bone loss was not significantly connected to healing at reassessment. On the other hand, the height of the buccal bone plate, according to Song *et al.* [47], was the only factor among periapical defects that actually influenced the healing outcome, concluding that the marginal bone deficiency was more significant than periapical bone deficiency to the outcome of EMS [47].

The reason for the poor prognosis may be the formation of a long junctional epithelium over the dehisced root surface since alveolar bone loss promotes the apical migration of gingival epithelial cells. The long junctional epithelium serves as a pathway for dissemination of microorganisms, preventing the healing process which may lead to the EMS failure [7,14,17,47].

To mitigate such a negative outcome, some studies perform regeneration techniques, such as guided tissue regeneration in order to promote better prognosis in endodontic-periodontal lesions

[7,8,11,15]. Six of the studies in the present review [8–10,15,17,48], resorted regeneration techniques in this type of lesions. The preferred materials were collagen resorbable membranes, such as Colla Tape® and BioMend®, and/ or bone substitutes, such as BioOss®, for guided bone regeneration procedures. Kim *et al.* [15] also associated calcium sulfate to CollaTape®. This material is extremely biocompatible, simple and effective [15]. Several studies proved that guided tissue regeneration in combination with EMS does not seem mandatory in teeth with intact alveolar bone surrounding the root surfaces [10]. However, it is expected to improve the healing outcome in teeth presenting "through and through" lesions [10] and those with complete buccal bone dehiscence, class F lesions by Kim and Kratchman, as confirmed by Zhou *et al.* [8] and Song et.al [9].

A successful EMS is assessed based on the radiographic resolution of the periapical radiolucency and the absence of clinical symptoms [33]. The studies included in this systematic review follow the criteria established by Rud *et al.* [55] and Molven *et al.* [56] for healing classification. In this review, outcome was dichotomised into success when complete and incomplete healing was attributed and failure when healing was uncertain and unsatisfactory.

In a Kim *et al.* study [15], classes D, E and F, which refers to endodontic-periodontal lesions according to Kim and Kratchman's classification, showed success rates of 77.5%, significantly lower than classes A, B and C, which evidenced 95.2% of success, with 2 to 5 years of follow-up. The high success rate of this study may be possibly associated to the advantages of the EMS and/or the use of regeneration techniques [15].

However, the fact that the success rate of endodontic-periodontal lesions was lower than isolated endodontic lesions, could lead to the assumption that endodontic-periodontal lesions show more failed cases over time. Notwithstanding, Song *et al.* [9] verified that among the 7 failure cases of the long-term follow-up, only one had periodontal involvement. This study was one of the two included studies to present a higher success rate for endodontic-periodontal lesions than isolated endodontic lesions.

In another study, Song *et al.* [47], while evaluating the impact of marginal bone loss on the outcome, a subgroup of 27 teeth with complete loss of the buccal bone plane (with marginal bone loss greater than 3 millimetres) was excluded from the analysis. As a result, the success rate shown for teeth with marginal bone loss greater than 3 millimetres is overestimated. If these subgroup of 27 cases, with 8 failures, were added to the 33 cases of marginal bone loss greater than 3 millimetres, the success rate would decrease from the presented 87,9% to a 80% success rate.

As for the studies of Huang *et al.* [48] and Yoo *et al.* [17], the low success rates of 50% and 33,3%, respectively, can be explained by the reduced sample size, 4 roots and 9 teeth, respectively. The validity of the reported lower success rate is weakened by a low recall rate as well as a considerable risk of bias.

In regard to the limitations of this systematic review, the first aspect to point out is the lack of geographical variability of the studies. The thirteen studies included correspond to six different research teams, one from Switzerland [13,49] and the others from Asian countries, such as Singapore [10,48], South Korea [9,11,14,15,17,19,47,50] and China [8], which indicates that the results obtained from this review should be carefully interpreted as they may not reflect the worldwide effectiveness of intervention. Secondly, the majority of studies have brought together cases from the Department of Conservative Dentistry of Yonsei University, in Seoul (South Korea) [9,11,14,15,19,47,50]. The Kim *et al.* study [15] is the basis for the other studies of this research team, given that the database is the same for all seven studies, it is very likely that there will be overlap in the samples of these studies, once some are follow-ups of one another. It is also possible to verify this last aspect in the von Arx.'s studies, since the 2012 study [49] corresponds to a 5-year follow up of the initial study [13]. All of the studies included in this review report evidence from academical clinical settings. In order to reflect the effectiveness of interventions in real-life routine conditions in general population, pragmatical clinical trials may be advantageous.

CONCLUSION

This systematic review and meta-analysis confirmed that the use of modern endodontic surgical techniques and materials is predictable and allows high success rates. It has also reached to the conclusion that isolated endodontic lesions or preoperative probing depths ≤ 3 mm were associated to higher success rates. According to the reviewed studies, the success rate of teeth with isolated endodontic lesions ranged from 78,2% to 95,3% whereas in endodontic-periodontal lesions it ranged from 67,6% to 88,2%.

This systematic review and meta-analysis concluded that periodontal attachment loss is a risk factor for the outcome for the EMS. Although, endodontic-periodontal lesions presented success rates lower than those found in isolated endodontic lesions, EMS performed in endodontic-periodontal lesions is a fully valid and viable procedure, allowing long-term success rates as revealed by the longer follow-up periods of the studies included.

Case selection for endodontic microsurgery should take into account the clinical importance of prognostic factors, such as periodontal involvement. Preservation of natural teeth should be the primary objective of endodontic microsurgery as a conservative approach. From a clinical point of view, as periodontal attachment loss is highly prevalent nowadays, it is mandatory to assess the level of bone support preoperatively. This assessment should be cautiously considered before the tooth undergoes the surgical procedure, in order to help in the decision-making process of extracting or preserving such teeth.

Future clinical studies should be conducted to evaluate the influence of the tooth type, single- or multi-rooted teeth, as well as the occlusal relationships in teeth with periodontal attachment loss on the prognosis of endodontic microsurgery.

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CONFLICTS OF INTEREST

There were no conflicts of interest in this project.

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SUPPLEMENTARY TABLES

Supplementary Table 1. Kim and Kratchman's classification of lesion types in endodontic surgical cases [12].

Class A	Absence of a periapical lesion, no mobility and normal probing depth, unresolved symptoms after nonsurgical therapies.
Class B	The presence of a small periapical lesion as well as clinical symptoms. Tooth with normal periodontal probing depth and no mobility.
Class C	Large periapical lesion progressing coronally without periodontal pocket and mobility.
Class D	Clinically similar to class C but with deep periodontal pockets.
Class E	Deep periapical lesion with an endodontic-periodontal communication to the apex and no obvious fracture.
Class F	Tooth with an apical lesion, complete absence of the buccal plate and no mobility.

Supplementary Table 2. Excluded studies after full-text reading

No.	Study	Exclusion criteria
1	Azim AA, Albanyan H, Azim KA, Piasecki L. The Buffalo study: outcome and associated predictors in endodontic microsurgery- a cohort study. International Endodontic Journal. 2021 Mar;54(3):301–18.	2
2	Wang ZH, Zhang MM, Wang J, Jiang L, Liang YH. Outcomes of endodontic microsurgery using a microscope and mineral trioxide aggregate: a prospective cohort study. Journal of Endodontics. 2017 May;43(5):694-698.	8
3	Kim S, Song M, Shin SJ, Kim E. A randomized controlled study of mineral trioxide aggregate and super ethoxybenzoic acid as root-end filling materials in endodontic microsurgery: long-term outcomes. Journal of Endodontics. 2016 Jul;42(7):997-1002.	2
4	Kim D, Ku H, Nam T, Yoon TC, Lee CY, Kim E. Influence of size and volume of periapical lesions on the outcome of endodontic microsurgery: 3-dimensional analysis using cone-beam computed tomography. Journal of Endodontics. 2016 Aug;42(8):1196–201.	8
5	Song M, Nam T, Shin SJ, Kim E. Comparison of clinical outcomes of endodontic microsurgery: 1 year versus long-term follow-up. Journal of Endodontics. 2014 Apr;40(4):490–4.	8
6	Shinbori N, Grama AM, Patel Y, Woodmansey K, He J. Clinical outcome of endodontic microsurgery that uses endosequence bc root repair material as the root-end filling material. Journal of Endodontics. 2015 May;41(5):607–12.	8
7	Song M, Kim E. A prospective randomized controlled study of mineral trioxide aggregate and super ethoxy-benzoic acid as root-end filling materials in endodontic microsurgery. Journal of Endodontics. 2012 Jul;38(7):875–9	2
8	Albanyan H, Aksel H, Azim AA. Soft and hard tissue remodeling after endodontic microsurgery: a cohort study. Journal of Endodontics. 2020 Dec;46(12):1824–31.	2,9
9	Taha NA, Aboyounes FB, Tamimi ZZ. Root-end microsurgery using a premixed tricalcium silicate putty as root-end filling material: a prospective study. Clinical Oral Investigations. 2021 Jan;311–317.	1,8
10	Chan S, Glickman GN, Woodmansey KF, He J. Retrospective analysis of root-end microsurgery outcomes in a postgraduate program in endodontics using calcium silicate–based cements as root-end filling materials. Journal of Endodontics. 2020 Mar;46(3):345–51.	2
11	Karan NB, Aricioğlu B. Assessment of bone healing after mineral trioxide aggregate and platelet-rich fibrin application in periapical lesions using cone-beam computed tomographic imaging. Clinical Oral Investigations. 2020 Feb;24(2):1065–72.	2,6

Supplementary Table 2. (Continued)

No.	Study	Exclusion criteria
12	Tawil PZ, Saraiya VM, Galicia JC, Duggan DJ. Periapical microsurgery: the effect of root dentinal defects on short- and long-term outcome. Journal of Endodontics. 2015 Jan;41(1):22–7.	2
13	Taschieri S, del Fabbro M. Endoscopic endodontic microsurgery: 2-year evaluation of healing and functionality. Brazilian Oral Research. 2009 Jan-Mar;23(1):23–30.	8
14	Song M, Shin SJ, Kim E. Outcomes of endodontic micro-resurgery: a prospective clinical study. Journal of Endodontics. 2011 Mar;37(3):316–20.	2
15	Schloss T, Sonntag D, Kohli MR, Setzer FC. A comparison of 2- and 3-dimensional healing assessment after endodontic surgery using cone-beam computed tomographic volumes or periapical radiographs. Journal of Endodontics. 2017 Jul;43(7):1072–9.	2
16	Li H, Zhai F, Zhang R, Hou B. Evaluation of microsurgery with supereba as root-end filling material for treating post-treatment endodontic disease: a 2-year retrospective study. Journal of Endodontics. 2014 Mar;40(3):345–50.	2
17	Pallarés-Serrano A, Glera-Suarez P, Tarazona-Alvarez B, Peñarrocha-Diago M, Peñarrocha-Diago M, Peñarrocha-Oltra D. Prognostic factors after endodontic microsurgery: a retrospective study of 111 cases with 5 to 9 years of follow-up. Journal of Endodontics. 2021 Mar;47(3):397–403.	2
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