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ORIGINAL ARTICLE/ARTICOLO ORIGINALE

Predictors of clinical outcomes in endodontic microsurgery: a systematic review and meta-analysis

Fattori predittivi del risultato clinico in microchirurgia endodontica: una revisione sistematica e meta-analisi

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Periapical surgery;
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Clinical factors.

Abstract The prevalence of recurrent periapical lesions has been reported between 43 and 65%, endodontic microsurgery (EM) is an alternative treatment option of recurrent periapical lesions.
Aim: the aim of the present study was to systematically quantify the effects of the association "clinical factors/follow-up period" on EM outcomes.
Methodology: Two researchers conducted a literature search from 2005 to 2015. Searched databases were MEDLINE, Evidence-based Endodontics, Cochrane Library, EMBASE, LILACS,

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PAROLE CHIAVE
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Fattori clinici.

SCIELO, Trip-Database. Tables of contents of endodontic journals and references listed on retrieved articles were searched as well. A residual heterogeneity test set at 95% confidence interval controlled sample variability of each study. Meta-regression estimated the factor/follow-up period on the outcomes of the ME.
Results: 1242 articles were identified, 10 of which were included for meta-regression. On average, EM was 84.13% successful when evaluated from 1 to 6 years. The heterogeneity analysis ($P = 0.87$) established the total variability of 8% in reference to sample variability. It was determined that a loss of "Crestal Bone Height" >3 mm proportionally predicts, from the second year on, an increased risk of EM failure (OR = 1.33, 90%CI, 1.01—1.77; $P = 0.09$). Factors such as "retro-filling material" ($P = 0.0002$), "presurgical clinical signs" ($P = 0.0116$), and "dentinal root defects" ($P = 0.0001$) are considered significant risk factors for EM failure without association to time.
Conclusions: EM could be considered clinically successful over time. The factor "crestal bone height" estimated a predictive and progressive association of healing from the second year on. Different root-end filling materials aside from MTA could be associated with EM failure, without association with follow-up periods.
*Registration Code: CRD42015029593, PROSPERO database.

Riassunto La letteratura riporta che la prevalenza delle lesioni periapicali ricorrenti si attesti tra il 43 e il 65%, la microchirurgia endodontica (EM) è un'opzione terapeutica alternativa per il trattamento delle lesioni periapicali ricorrenti.
Obiettivi: Lo scopo di questo lavoro era di quantificare in modo sistematico gli effetti dell'associazione tra fattori clinici e periodo di follow up sui risultati ottenuti dalle terapie di EM.
Materiali e metodi: Due ricercatori hanno compiuto una ricerca bibliografica che ha compreso gli articoli pubblicati tra il 2005 e il 2015. I database consultati erano MEDLINE, Evidence-based Endodontics, Cochrane Library, EMBASE, LILACS, SCIELO, Trip-Database. Sono anche stati consultati gli indici dei giornali endodontici e gli elenchi di riferimenti bibliografici citati negli articoli selezionati. Un test di eterogeneità residua con un intervallo di confidenza del 95% ha controllato la variabilità dei campioni presi in considerazione in ciascuno degli studi selezionati. Una meta-regressione ha stimato l'effetto del rapporto fra fattori e periodo di follow up sui risultati ottenuti dai trattamenti di ME.
Risultati: Sono stati identificati 1242 articoli, 10 dei quali sono stati esaminati con la meta-regressione. Mediamente EM, valutata in un periodo compreso tra 1 e 6 anni, ha riportato una percentuale di successo dell'84.13%. L'analisi di eterogeneità (P = 0.87) ha stabilito l'esistenza di una variabilità dell'8% dei campioni. È stato determinato che una perdita nell'"altezza dell'osso crestale" superiore a 3 mm faccia presagire in modo proporzionale, dal secondo anno di osservazione in poi, un aumento del rischio di fallimento dell'EM (OR = 1.33, 90%CI, 1.01-1.77; P = 0.09). Fattori come "materiale da otturazione retrograda" (P = 0.0002), "segni clinici pre-chirurgia" (P = 0.0116), e "difetti nella dentina radicolare" (P = 0.0001) sono considerati fattori di rischio significativi per il fallimento dell'EM, indipendentemente dal periodo di follow up.
Conclusioni: EM si può considerare una terapia che riscuote il successo clinico nel tempo. Il fattore "altezza dell'osso crestale" è associata alla guarigione in modo predittivo e progressivo a partire dal secondo anno. Materiali da otturazione retrograda diversi dall'MTA possono essere associati al fallimento della terapia di EM, indipendentemnte dal periodo di follow up osservato.

Introduction

Post-treatment periapical disease (PPD) is characterized by the presence of periapical pathology, which may be emergent, recurrent, or persistent.[1] According to some clinical studies,[2] its prevalence ranges from 43 to 65%, and it is generally associated with poor endodontic or restorative treatments, which facilitates the presence of pathogenic microorganisms resistant to the chemical-mechanical preparation of the root canal, thus allowing them to adapt during long periods of time to the sealed root canal.[1] Therefore, a second endodontic intervention is necessary to restore health of the periapical tissues. In this sense, endodontic microsurgery (EM) becomes an alternative approach that should be considered when root canal ortograde retreatment is contraindicated.[3]

The success rate of EM varies from 78 to 92%.[4,5] Nevertheless, that given the heterogeneity of the treatment protocols employed, the multiple risk factors that condition to the outcomes of surgical treatment, in addition to the difficulties related to proper follow-up schemes,[5] altogether challenge the researchers' ability to unequivocally demonstrate the effectiveness of EM to eliminate PPD. Current research has established an association between clinical factors and EM outcomes.[6,7] In fact, the status of the supporting bone,[4] size of the apical lesion,[8] presence of preoperative pain,[4,9] quality of retrograde root canal filling,[4,10] and condition of coronal restoration[4,9,10] are determinants of periapical healing.

It should be noted that the risk posed by each factor and its relationship with the follow-up period has not been sufficiently studied. This association, therefore, must be investigated. In this regard, two philosophies are in vogue today. One the one hand, some studies[11,12] support the concept that a preliminary result observed in a short follow-up period could be considered predictive of final result over time. On the other hand, the term "post-surgical recurrence" is employed when failure occurs in teeth that are either healed or in the process of healing, when observed at sizable follow-up periods.[4,7]

In order to determine the association between post-surgical healing predictors and follow-up, the subsequent Patient-Intervention-Comparison-Outcome (PICO) question was formulated: What is the effect of clinical factors on EM outcomes in teeth with Post-treatment periapical

disease, when evaluated over different periods of time? A search in the Prospero[13] and the Cochrane Collaboration[14] databases did not retrieve any previous research addressing this subject.

Materials and methods

The methodology implemented for the present investigation was based on "The Institute of Medicine Standards for a Comprehensive Search"[15] and "The Cochrane Handbook for Systematic Reviews of Interventions".[16] The protocol was registered in the PROSPERO database (Registration Code: CRD42015029593).

Eligibility criteria

Inclusion criteria were:

- Type of study: randomized controlled trials (RCTs) and non-randomized trials (NRTs) published between 2005 and 2015 that analyzed longitudinally clinical factors with at least 1 year of follow-up.
- Type of population: studies performed in human subjects using permanent teeth as study unit.
- Type of intervention: studies using EM as a modality of treatment, according to the criteria established by Kim and Kratchman.[8] EM was assessed in accordance with the categories outlined by Rud et al.,[17] and Molven et al.[18]

Search strategy

An electronic search of the English and Spanish literature was performed. From September 2014 to August 2015, 2 investigators (CGG and SQG) searched the following databases: MEDLINE via PUBMED, Evidence-Based Endodontics Literature Database, The Cochrane Oral Health Group's Trials Register (CENTRAL), EMBASE via OVID, LILACS, SCIELO via BIREME, and Trip Data Base. In order to identify prognostic studies (cohort, incidence, follow-up studies, prognos*, predict*, or course), a highly-sensitive search was implemented according to the recommendations of Hayden et al.[19] Secondary searching (PEARLing) was conducted. Additionally, table of contents of the following journals were reviewed: International Endodontic Journal, Journal of Endodontics, Oral Surgery Oral Medicine Oral Pathology Oral Radiology, and Restorative Dentistry and Endodontics. Ongoing trials were revised by searching in The Meta Register of Controlled Trials (http://www.controlled-trials.com) and The US National Institutes of Health registry (http://www.clinicaltrials.gov)[20] databases.

Medical Subject Headings (MeSH) and the Spanish version of MeSH, "Descriptores en Ciencias de la Salud" (DeCS) were employed. MeSH were searched in English and DeCS in Spanish. Boolean operators OR and AND were used as well. (("endodontics/endodoncia" OR "microsurgery/microcirugía" OR "periapical surgery/apicectomía" OR "surgical endodontic treatment" OR "root-end surgery")) AND ("clinical factors" OR "predictors outcome") AND ("longitudinal studies" OR "randomized controlled trials as a subject") AND ("assessment outcomes" OR "prognosis").

Selection process

Initially, one reviewer (CGG) examined the titles for further reading of the abstracts. A record by search date monitored the systematization process. Selected abstracts were analyzed independently by 2 investigators (CGG, SQG). Those abstracts meeting the inclusion criteria were selected and the articles read in full; the approval of at least one evaluator was enough to consider it. Any disagreement regarding the inclusion of a given study was resolved through consensus and in some cases through the concept of a third evaluator (DMZ). Fig. 1, shows the algorithm used during the search and selection process.

Quality assessment and bias analysis

Once the articles were selected, internal validity was established by controlling bias analysis using the tool suggested by the Cochrane Collaboration.[21] Subsequently, the quality of the evidence was defined by applying the tool proposed by the National Institute for Health and Care Excellence (NICE),[22] as shown in Fig. 2.

Data analysis

The following characteristics of each study were evaluated: design, sample size, clinical factors, follow-up period, and success/failure rate according to post-surgical healing.

For qualitative analysis purposes, the results were grouped in the following manner:

- Outcomes of EM. Dichotomized in 2 categories:
  - Success: complete or incomplete healing.
  - Failure: unsatisfactory or uncertain healing.[18]
- Clinical factors. Grouped according to:

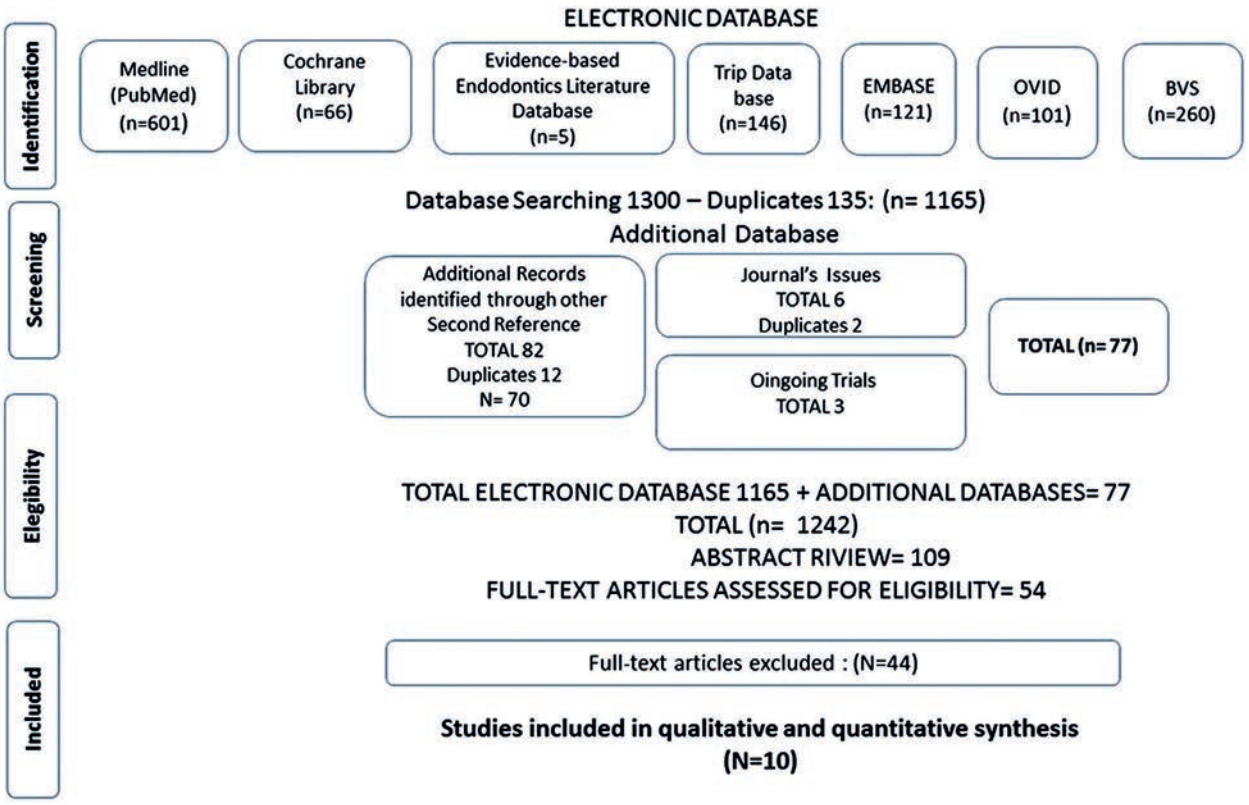

Figure 1 Flow chart depicting the selection process of the articles.

- Patient: age, sex, smoker.
- Tooth: type and location of tooth within the arcade.
- Pain and/or pre-surgical clinical signs: Inflammation, fistula, root dentinal defects.

• Supporting tissues. Categorized according to:
- Size (>5 mm ≤) and type of lesion (lesion of endodontic origin vs lesion of combined endodontic-periodontal origin).
- Type of pathology (post-surgical histologic assessment).

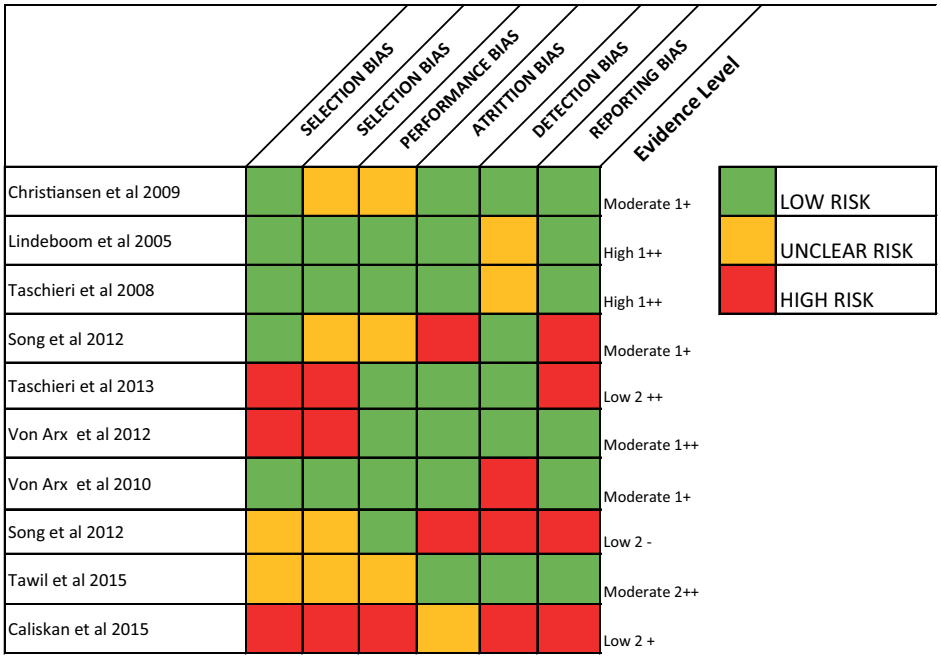

Figure 2 Quality assessment and risk of bias graphic.

- Crestal bone level: was defined by von Arx et al., 2012,[4] as the distance between the interproximal bone level and the cementoenamel junction. The Crestal bone level, was classified in: mesial and distal ≤ 3 mm, mesial and distal > 3 mm, mesial or distal >3 mm, according to the categories described by von Arx et al., 2012.[4]

• Type of treatment. Grouped according to:
- Quality and length of root canal filling.
- Presence of post.
- Type of endodontic treatment (apical surgery, previous retreatment).
- Magnification technique.
- Retrograde root canal filling.
- Post-surgical antibiotic prescription.
- Immediate post-surgical healing.

Finally, the percentage of healing for each factor in relation to the follow-up period was established. The synthesis of the data was recorded in contingency tables for further statistical analysis.

Statistical analysis

A descriptive analysis measured the relationship between studied factors, follow-up period, and outcomes of the procedure. The outcomes of EM ''successful'' or ''failure'' of each factor were recorded as a dichotomous data. A forest plot graphic represented the significant changes in the ORs of the surgical factors over time that were calculated by using a fixed-effect meta-regression, which was adjusted for those surgical factors that had been previously analyzed in more than two points in time (13/21). For those factors providing a preliminary analysis in only one or two points in time (8/21), a fixed-effect model was adjusted without time significance because the number of points in time could act as causal false of the perfect fit model.

To assess the influence of an individual study on the pooled effect, statistical heterogeneity analysis was assessed. A residual heterogeneity test was performed in order to control the total variability of the estimated effect of the meta-regression model and the sampling variability provided by each study. The null hypothesis stated that the heterogeneity of the real logarithms ORs, (log ORs) was zero (Hotau?2 = 0). All calculations were made using the R statistical software [http://www.r-project.org/], version 3.2.2, Metafor package [Http://www.jstatsoft.org/v36/i03/].

Results

After the application of eligibility criteria, a total of 1242 titles were identified; 10 of them were included for qualitative and quantitative analysis (Table 1). Fig. 1 shows the Preferred Reporting Items for Systematic

Reviews and Meta-Analysis (PRISMA) study flow diagram. The final sample included a total of 1402 teeth treated by means of EM. Table 2 shows excluded papers and the reasons behind the exclusion.

Descriptive analysis of selected studies

The 10 selected papers were characterized according to:
• Year of publication: 2005—2015.
• Type of study: 4 RCTs,[23—26] 1 cohort,[4] 4 prospective case series,[11,12,27,28] and 1 retrospective study.[29]
• Geographic area of the studied population: Netherlands,[25] Italy,[23,29] Denmark,[26] Switzerland,[4,27] South Korea,[12,24] United States of America,[11] and Turkey.[28]
• Journal: Oral Surgery Oral Medicine Oral Pathology Oral Radiology,[25] International Journal of Oral and Maxillofacial Surgery,[23] International Endodontic Journal,[26,28] Journal of Endodontics,[4,11,12,24,27] and Australian Endodontic Journal.[29]

Bias analysis of selected studies

Fig. 2 depicts bias evaluation and level of evidence for each included study. The Cochrane Collaboration ''Risk of Bias'' tool was used to assess the methodological quality of the included studies.[30] Of note, 60% of the studies had a high risk of bias in at least one of the analyzed aspects.

Data analysis

Heterogeneity analysis

Residual heterogeneity test (H^2) ($p = 0.8767$) determined, with a 95% confidence level, that there was enough statistical evidence to accept the null hypothesis, Ho (Hotau?2 = 0), confirming that 100% of the total variability was captured by the fixed part of the model (simple variability) and that only 8% of the estimated effect between the clinical factors and EM outcomes observed over time had been randomly modified.

Healing over time

The average rate of successful post-surgical healing reported by each study according to the follow-up period was: 83% (first year), 85.5% (second year), 73.12% (third year), 88.81% (fourth year), 84.9% (fifth year), and 89.5% (sixth year).

Meta-analysis of healing considering the follow-up period

A descriptive analysis confirmed the possibility to analyze the trend of the OR for the selected surgical factors over time. The fixed effects model determined that factors such as ''Retrograde Root Canal Filling'' (OR = 2.75; CI, 1.61—4.70; $P = 0.0002$) and ''Presence of Preoperative Clinical Signs'' (OR = 3.10; CI, 1.28—7.48; $P = 0.0116$) represented significant risk factors in Time One (Fig. 3A and B). Conversely, the pre-surgical factor ''Crestal Bone Level'' (OR = 1.33; 90% CI, 1.01—1.77; $P = 0.09$) influenced the outcome of EM over time, suggesting that a decrease in the ''Crestal Bone Level'' does not represent a risk for postsurgical healing during the first year, but as the follow-up increases (2—6 years), it behaves as a prognostic factor that reduces the success rate of EM (Figs. 3C and 4).

On the other hand, factors such as ''Age'' (OR = 0.86; CI, 0.66—0.12; $P = 0.27$), ''Sex'' (OR = 0.88; CI, 0.70—1.10; $P = 0.28$), ''Type of Tooth'' (OR = 1.12; CI, 0.93—1.35; $P = 0.19$), ''Location of Tooth '' (OR = 0.97; CI, 0.81—1.16; $P = 0.74$), ''Presence of Preoperative Clinical Signs'' (OR = 0.81; CI, 0.64—1.04; $P = 0.10$), ''Size of Apical Lesion'' (OR = 1.06; CI, 0.84—1.33; $P = 0.58$), ''Previous Apical Surgery'' (OR = 0.96; CI, 0.69—1.32; $P = 0.81$) ''Length of Root

Table 1 Study characteristics.

Author	Study type	Outcome (%)	Factors	Significant factor	Time in years	n	OR	IC	*P* value
Lindeboom JA, 2005. Netherlands[25]	ECA*	89	Retrograde Root Canal Filling	MTA vs IRM	1	100	1.8	—	>0.05
Taschieri S, 2008. Italy[23]	ECA*	91	Type and Location Tooth, Magnification	Magnification Micro vs Endosc	2	100	1.16	—	0.16, 0, 50, 0.13
Christiansen R, 2009. Denmark[26]	ECA*	74	Retrograde Root Canal Filling	MTA vs GP¥	1	46	—	—	0.001
von Arx T, 2010. Switzerland[27]	Prospective case series	85.5	Retrograde Root Canal Filling, and preparation type. Type and Location Tooth, Post.	MTA vs Retroplast	1	339	3.34	—	0.003
Song M, 2012. South Korea[24]	ECA*	94.3	Age, Sex, Type Tooth, Retrograde Root Canal Filling	MTA vs SuperEBA	1	192	1.58	—	0.472
Von Arx T, 2012. Switzerland[4]	Cohort	83.8	Age, Sex, Smoker, Type and Location Tooth, Pain, Presence of Preoperative Clinical Signs, Lesion Size, Crestal Bone Level, Length of Root Canal Filling, Post, Re-surgical, Post-Surgical Antibiotic, Retrograde Root Canal Filling, Immediate Postsurgical Healing.	Presence of Preoperative Clinical Signs	1	191	—	1.20—5.58	0.04
		75.9	Age, Sex, Smoker, Type and Location Tooth, Pain, Presence of Preoperative Clinical Signs, Lesion Size, Crestal Bone Level, Length of Root Canal Filling, Post, Re-surgical, Post-Surgical Antibiotic Retrograde Root Canal Filling, Immediate Postsurgical Healing.	Mesial-distal crestal bone level (0 = >3 mm,1 = #3 mm)	5	170	5.10	1.67—16.21	0.017
		75.9	Age, Sex, Smoker, Type and Location Tooth, Pain, Presence of Preoperative Clinical Signs, Lesion Size, Crestal Bone Level, Length of Root Canal Filling, Post, Re-surgical, Post-Surgical Antibiotic Retrograde Root Canal Filling, Immediate Postsurgical Healing.	Retrograde Root Canal Filling SuperEBA vs ProRoot MTA.	5	170	7.65	2.60—25.27	0.003

Table 1 (*Continued*)

Author	Study type	Outcome (%)	Factors	Significant factor	Time in years	n	OR	IC	*P* value
Song M, 2012. South Korea[12]	Prospective case series	93.3	Lesion Type	EndoPeriod vs Endo only	6	104	1.76	—	>0.05
Taschieri S, 2013. Italy[29]	Retrospective	91.5—91.9	Age, gender, Post, Type and Location Tooth, Lesion Size, Magnification	Magnification Microsc vs Loupes	1—4	86	2.1	0.31—13.95	>0.05
Çalışkan MK, 2015. Turkey[28]	Prospective case series	80	Age, Sex, Location Tooth, Lesion Size, Post, Obturation quality, Type of treatment, Re-surgical, Type Pathology, Post-Surgical Antibiotic, Immediate Postsurgical Healing.	No significativ.	2	90	—	—	>0.05
		82.7			3	90	—	—	>0.05
		85.7			4	90	—	—	>0.05
		85.7			5	90	—	—	>0.05
		85.7			6	90	—	—	>0.05
Tawil PZ, 2015. United States of America[11]	Prospective case series	62.3	Age, Sex, Location Tooth, root dentinal defects Material de retrobt Super EBA vs MTA.	root dentinal defects	1	134	42.9	0.50—0.77	<0.0001
		63.55	Age, Sex, Location Tooth, root dentinal defects Material de retrobt Super EBA vs MTA.		3	127	77.2	0.00—0.06	< 0.0001

ECA*: randomized clinical trial. GP¥: smoothing of the orthograde gutta-percha root filling.

Table 2 Excluded Studies with Reasons for Exclusion from the Meta-analysis.

Study	Exclusion criteria	Study	Exclusion criteria	Study	Exclusion criteria	Study	Exclusion criteria
Lui JN, 2014	3, 6, 10, 11, 12, 15	Iqbal MK, 2007	13	Del Fabbro, 2009	9, 13, 14, 15, 17	Estrela C	6, 7, 18
Li H, 2014	14	Von Arxz, 2011	14	Kim E, 2008	8	Tortorici S, 2014	3, 6, 7, 12
Von Arx t, 2007	3, 7, 9, 14	Taschieri S, 2011	14	Taschieri S, 2006	8, 14	Bill Kalher, 2010	2
Song M, 2013	6, 8, 14	Barone C, 2010	12, 16	Peñarrocha-Diago M, 2012	3, 7, 8	Yazdi PM, 2007	3, 6, 7
Song M, 2013	3, 8, 9, 14	Érica Gouveia J, 2015	14	Peñarrocha M, 2011	8, 12, 15	Gagliani MM, 2005	9
Song M, 2011	8, 14	Sánchez-Torres A, 2014	14	Ortega-Sánchez B, 2009	3, 7, 8, 12	Kreisler M, 2013	7, 10, 11
Baek SH, 2010	5	Bernabe PF, 2013	3	Carrillo C, 2008	8, 12, 14	Wang Q, 2004	9, 17
Karabucak B, 2009	2, 3, 7, 14	Tanomaru-Fllho M, 2015	14	Peñarrocha Diago M, 2007	8, 12, 14	Shen J, 2012	4
Taschieri S, 2009	7, 14	Del Fabbro, 2012	13, 14, 15	Pljevljak N, 2011	12	Chong BS, 2003	9
Tawil PZ, 2009	5, 13	Garip H, 2011	1	Goyal B, 2011	3, 6, 7	da Silva SR, 2015	6, 13
de Ruiter MHT, 2014	4	Von Arx T, 2007	8	Song, 2014	14	Saunders 2008	11, 14

1. In vitro study. 2. Case report studies. 3. High risk of bias. 4. Not available. 5. Animal Study. 6. High attrition rate or unrepresentative sample size. 7. Inappropriate methodological design. 8. The study was based on a population that was part of an earlier publication. 9. Does not meet the inclusion criteria. 10. Does not include Ethical criteria. 11. Unrepresentative statistical analysis to estimate the effect. 12. Retro-obturation material does not include in ME. 13. A following up <1 year. 14. Does not answer the question. 15. Assessment criteria of success and failure different from the selected for this study. 16. Techniques that did not fit the specific criteria defined for ME. 17. Survival studies.

Canal Filling'' (OR = 0.88; CI, 0.66—1.17; $P = 0.40$), ''Presence of Post'' (OR = 1.07; CI, —0.88—1.28; $P = 0.47$), ''Retrograde Root Canal Filling'' (OR = 0.93; CI, 0.77—1.12; $P = 0.45$), ''Post-Surgical Antibiotic Medication'' (OR = 1.10; CI, 0.85—1.42; $P = 0.43$), and ''Immediate Postsurgical Healing'' (OR = 0.97; CI, 0.70—1.35; $P = 0.89$) were not associated with the risk of EM failure over time.

Meta-analysis of healing without considering the follow-up period

For factors ''Quality of Sealing'', ''Pre-surgical Pain'', ''Root Dentinal Defects'', ''Smoking Status'', ''Magnification Technique'', ''Type of Lesion'', ''Type of Pathology'', and ''Type of Endodontic Treatment'', it was not possible to establish an association with the follow-up period. It was found, however, that ''Root Dentinal Defects'' (OR = 52.98; CI, 21.11—132.95; $P = 0.0001$) behaved as a factor that decreased the probability of EM success.

Discussion

This systematic review measured the effects of clinical factors as prognostic predictors of EM outcomes when studied over time. The search considered studies published since 2005. The probability of success for EM is 1.58 times higher than that of traditional endodontic surgery.[31] This situation excluded 15% of articles read in full, including the study of Barone et al.,[32] which clearly answered the research question, but did not guarantee that the entire population was treated by means of EM. A consensus regarding postsurgical evaluation criteria according to Rud et al.,[17] and Molven et al.,[18] allowed homogeneity in the evaluation of the outcome variable (success or failure), this being enough reason to exclude 9% of the studies that did not meet this criteria. Equally, 27% of the studies had methodological weaknesses that increased the risk of bias at the time of evaluation.

In general, an average rate success of 84.13% was established for the selected studies, which evaluated EM from 1 to 6 years. This result shows a reduction of 5—10% in success rates when compared to the results of Kang et al. (92%),[5] Tsesis et al. (89%),[7] and Setzer et al. (94%).[31] More than 50% of the primary studies supporting the results of previous meta-analyzes had follow-ups inferior to 2 years. The percentage found in this study is in agreement with previous research showing that healing percentages slightly decrease from the second year on. Once all 10 studies were evaluated and the factors for the meta-regression analyzed, it was determined that the ''Crestal Bone Level'' behavied as a co-variable (time-dependent), since the probability of failure was higher for teeth with reduced bone level previous to EM.

In EM, and generally in endodontics, it is difficult to get long-term adherence.[5] Considering the results of EM according to the follow-up, two philosophies were identified. The first one established that results found at 1 year of follow-up might be predictive of results at longer follow-ups.[33,34] That is, EM can be considered a stable procedure over time. Rubinstein et al.,[35] observed a steady trend rate of success (91.5%) in EM after 7 years of follow-up. Song et al.,[33] stated that more than 90% of healing during the first year could be comparable to the 87.8% at four or more years of evaluation. This percentage difference is not statistically significant

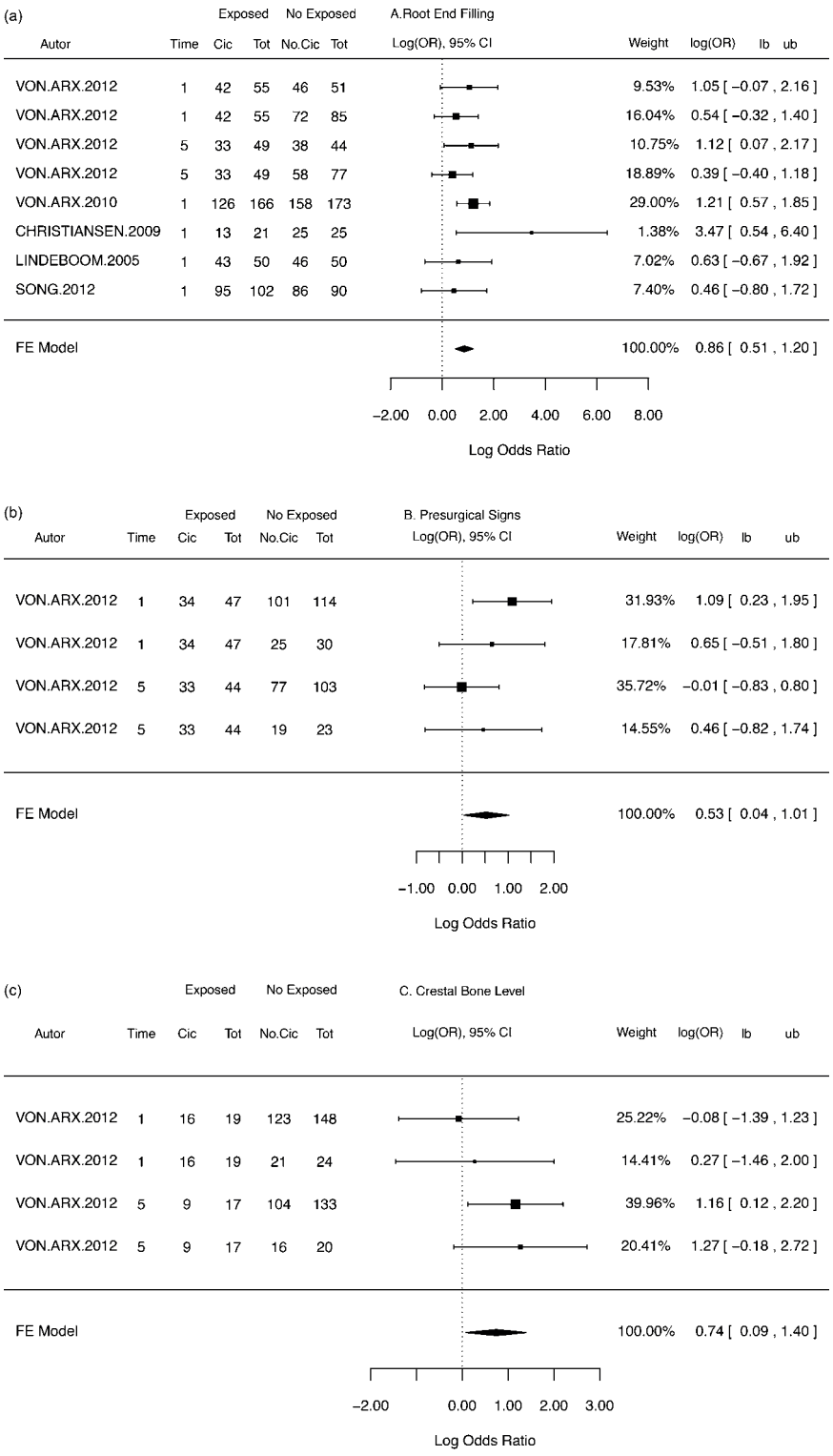

Figure 3 Forest plots of ORs at different times: (A) root end filling, showing healing changes on the first year only. (B) Presurgical signs, showing healing changes on the first year only. (C) Crestal Bone level, showing healing changes after 5 year of follow-up.

($P = 0.344$), which confirms the thesis that time does not imply an additional risk for EM outcomes. These findings probably led to reports of EM limited to short follow-up periods (1—2 years), which was reflected in this study, where 25 papers out of 54 selected for full text reading showed results with follow-up periods inferior to 2 years.[36—57]

The second philosophy states that short follow-ups do not document the recurrence of apical periodontitis, which occurs even after apparent complete healing.[32] This ''recurrence'' of periapical disease has been estimated between 5 and 25%.[58] Qualitative observation of the relationship between predictive factors and EM

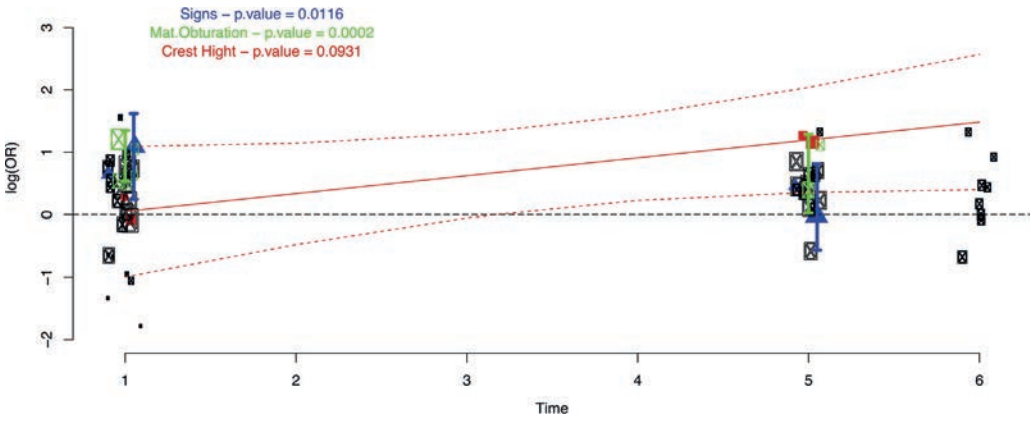

Figure 4 Effects of clinical factors on periapical healing over time; they were considered significant. ''Root end filling'' (green), ''Presence of preoperative clinical signs'' (blue), and ''crestal bone height'' (red). The dot size indicates the way in which the study is weighted according to its variance and to the quality of the information (big dots indicate less variability and more information, while small dots indicate greater variability and less information).

outcomes at different follow-ups shows percentage differences in selected studies, which marked a trend towards success or failure, thus justifying the present meta-analysis. In this sense, von Arx et al.,[4] reported how a preliminary 1-year result could define the behavior of healing when observed at greater follow-up periods, as long as the result is directly related to a predictive factor. Therefore, the decrease in EM success rate would be conditioned by the presence of a risk factor modifying the result.

In the present investigation, the ''Crestal Bone Level'' (OR = 1.33, 90% CI, 1.01—1.77; $P = 0.09$) proved to be a prognostic factor that, associated to the follow-up period, influenced the healing process. The model predicted how, after the first year of evaluation, teeth with reduced crestal bone level proportionally reduced the probability of EM success (Fig. 4), demonstrating how the association factor/outcome becomes more evident as time goes on. Although the obtained value did not show a great association, it is important to note that this observation is consistent with Kim et al.,[59] who in 2008 estimated a decreased success rate of 17.7% for cases with tissue alterations previous to EM, when compared to teeth that did not have evident damage of the supporting tissues.

Using a finite-element model, Jang et al.,[60] proved that a crestal bone level greater than 3 mm resulted in a reduction of the ability to support masticatory loads, as much as if the root length decreased 4—6 mm with apicectomy; thus considering that the results of EM depend on multiple factors that, together, determine success. The ''Crestal Bone Level'', depending on the follow-up period, was considered as a prognostic factor for post-surgical success. Therefore, when a decrease in crestal bone level is present, short follow-up periods might overestimate the actual success rates, which can be achieved with longer follow-ups.

Primary studies defined that ''Age'',[32] ''Size of the Apical Lesion'',[8] ''Presence of Preoperative Pain'',[4,9] ''Type of Retrograde Root Canal Filling'',[4] ''Quality of Retrograde Sealing'',[10] among other factors, are determinative of EM outcomes. This justified the analysis of the clinical factors proposed in each of the selected studies for this meta-analysis using statistical power. The results confirmed that clinical factors predictive of EM outcomes (not related to follow-up) were ''Presence of Root Dentinal Defects'' ($P < 0.0001$), ''Presence of Preoperative Clinical Signs'' ($P = 0.011$), and ''Retrograde Root Canal Filling'' ($P = 0.0002$). In this regard, Tawil et al.,[11] reported a 65% decrease in success rates posterior to EM for teeth having root dentinal defects.

In the present study, ORs = 52.98 estimated that 40% of teeth presenting root dentinal defects had the chance of failure. This statement may be obvious, taking into account the damage caused by cracks into the root dentin. On the other hand, it was confirmed that the presence of preoperative clinical signs decreased healing during the first year of follow-up without altering EM outcomes when followed during longer periods.[6] Similarly, the ''Retrograde Root Canal Filling'' factor confirmed that the use of materials different from MTA pose a risk for EM failure. By including the ''Time'' variable, differences that could represent a significant clinical risk ($P = 0.45$) were not observed. These findings controvert those by von Arx et al., where the use of Super-EBA generated a 19% decrease in success rates in 5 years (OR = 7.65; CI, —2.60—25.27; $P = 0.004$), when compared to the healing results obtained with MTA.[4]

In addition, factors such as ''Sex'', ''Age'', ''Smoker'', ''Preoperative Pain'', ''Type and Location of Tooth'', ''History of Apical Surgery'', ''Limit of Apical Obturation'', ''Presence of Post'', ''Magnification Technique'', ''Antibiotic Medication'' and ''Post-Surgical Complications'' proved not to be determinants of healing in EM. Regarding the ''Size of the Lesion'', von Arx et al., [4] found that lesions greater than 5 mm did not present differences in healing percentages the first year when compared to smaller lesions. However, at a 5-year follow-up, their healing probability is 12% less. Another study concludes that, during the first four years of follow-up, lesion size proportionally alters the healing process ($P = 0.02$).[61] Other papers report that the ''Size of the Crypt'' could be a significant outcome predictor ($P = 0.008$) after 4 years or more.[32] However, this risk factor is not significant for healing when observed over longer periods,[32] a finding that is consistent with the results of the present investigation.

Finally, two methodological conditions were identified: A) from 2 to 6 years. It was not possible to group more than 2—3 studies per follow-up period, B) for longer follow-ups, the

number of teeth were proportionally reduced in relationship to the baseline. This suggests that authors supporting the concept of short follow-up periods predictive of EM outcomes have methodological weaknesses that overate the results.[11,12,33–35] Research groups that support long-term follow-up periods have difficulties with sample monitoring, thus generating lack of clarity in the presentation of the results with consequent high reporting bias.[12,24,28]

Conclusions

According to the success rates studied at different follow-up periods, EM can be considered a clinically effective treatment for the management of PAP. EM outcomes could be modified over time according to variables that modify healing. In the present investigation, the crestal bone level was related to outcomes in the sense that a decrease in crestal height was considered as an indirect prognostic factor predictor of EM failure. Similarly, factors such as root dentin defects, presence of preoperative clinical signs, and retrograde root canal filling behavied as outcome predictors. Their influence at greater healing periods, nevertheless, was not evident.

Recomendations

It is necessary to design clinical studies that aim at determining the role of crestal bone level and its interactions with other risk factors that may influence the outcomes of EM.

Conflict of interests

The authors have no conflicts of interest to declare.

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