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SYSTEMATIC REVIEW

Regenerative Endodontic Procedures in Teeth with Root Resorption: A Systematic Review

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ABSTRACT

The purpose of this systematic review was to critically evaluate the available clinical literature on the use of regenerative endodontic therapy (RET) for the treatment of root resorption. All case reports, case series and clinical studies documenting the management of root resorption in mature or immature permanent teeth using RET were included. Review articles, animal studies, and RET in teeth showing developmental anomalies were excluded. A literature search was conducted in electronic databases MEDLINE, Scopus, Cochrane, and Google Scholar from 2001 to January 2022. The JBI Critical Appraisal Checklist Quality was used to appraise the included case reports and case series. The Methodological item for non-randomised studies (MINORS) tool was used to appraise the clinical study critically. After applying the inclusion and exclusion criteria, the search resulted in 14 studies (12 case reports, 1 case series, and 1 clinical study) accounting for root resorption in 34 teeth from 29 patients treated with RET. Despite the wide variation in RET protocols, the arrest of root resorption and resolution of symptoms was seen in all teeth except one (failure after 27 months). The clinical study's cone beam computed tomography (CBCT) imaging evaluation documented a significant volumetric decrease in resorptive and periapical lesions after RET. The clinical study was deemed as good quality using the MINORS scale. The JBI critical appraisal tool showed that the case series was of poor quality; 11 of the case reports were of good quality, while 1 case report was of fair quality. This systematic review revealed a low-to-moderate level of evidence for the use of RET in resorption cases. However, further well-designed, long-term clinical studies are required to recommend it as an alternative treatment option for root resorption management. Funding: None. The systematic review was registered in PROSPERO (CRD42021274569).

Keywords: Case reports, regenerative endodontics, reparative endodontics, root resorption, systematic review

HIGHLIGHTS

- Contemporary treatment protocols for root resorption manage to arrest the progress of the resorptive process but fail to compensate for the lost tooth tissue.
- Hence, RET is considered a valuable treatment option for cases of root resorption. This systematic review has evaluated the strength of the clinical recommendation based on currently available clinical evidence.
- Further well-designed, long-term clinical studies are required to recommend it as an alternative treatment option for root resorption management.
- However, RET may provide a viable treatment option in cases of teeth with severe resorption or replacement resorption where the prognosis is guarded.

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INTRODUCTION

Resorption is a condition associated with either a physiologic or a pathologic process resulting in a loss of dentine, cementum, or bone (1). Unlike primary teeth, permanent teeth seldom undergo root resorption. This may be attributed to the fact that in a healthy tooth, the cementum and predentine deter the attachment of the osteoclasts. However, a prolonged inflammatory response in the pulp or periodontal tissue due to various causes like trauma, periodontal infections, caries-induced pulpitis, orthodontic treatment, calcium hydroxide (CH) capping, etc., may damage or alter these tissues (2). This may, in turn, trigger a destructive phase in which active root resorption occurs due to the activation of the RANK-RANKL-OPG system (RANK: receptor activator of nuclear factor; RANKL: receptor activator of nuclear factor ligand; OPG: osteoprotegerin), which results in osteoclastogenesis (3, 4).

While epidemiologic data on internal inflammatory root resorption is scarce, its prevalence has been reported between 0.01–1% (5). External inflammatory resorption occurs in 5–8% of teeth after luxation injuries, 30% of replanted teeth after avulsion, and 38% of intruded teeth (2). The frequency of replacement root resorption was reported to be 51% in avulsion cases (6) and 57.1% in intrusive luxation cases (7).

Teeth with internal and external resorption have been classified as "high difficulty" by the American Association of Endodontists (AAE) Endodontic Case Difficulty Assessment Form and Guidelines because achieving a predictable treatment outcome in such cases can be challenging (8). In addition, treatment of root resorption varies according to type, location, progression, and prognosis (9).

External inflammatory root resorption can be managed by disinfection of root canal space using intracanal medicaments like CH and demeclocycline hydrochloride plus triamcinolone acetonide (Ledermix® paste, Lederle Pharmaceuticals, Wolfratshausen, Germany) followed by root canal treatment (9). When replacement resorption sets in, no currently available therapies can arrest it. If such a tooth in the developing dentition becomes unrestorable, then intentional decoronation may be the only possible treatment to prevent the under-development of the alveolar ridge (2). For cases of internal inflammatory resorption, activated sodium hypochlorite (NaOCl) and intracanal CH, followed by thermoplasticised gutta-percha obturation, are recommended (10). In cases of perforation, bioactive hydraulic silicate cements are usually used to repair the resorptive defect. When the perforating defects are not amenable to internal repair, a surgical approach is often the choice (2).

There are several limitations to current treatment protocols for the management of resorption. First, they only manage to arrest the progress of the resorptive process. When long-term intracanal CH is used, the susceptibility of the tooth to fracture increases (11). The thermoplasticised technique, when used for obturation in cases with internal resorption, may be susceptible to sealer dissolution and voids (12). Another challenge is the flowability of the sealing material within the resorptive defect (10). More importantly, compensating for the lost tooth tissue does not occur after traditional treatment approaches for root resorption. Hence, in cases of teeth with severe resorption or perforation, the prognosis is poor, prompting clinicians to opt for extraction as the treatment of choice.

In 2001 Iwaya et al. (13) reported the technique of 'revascularisation' on an infected immature permanent tooth. Disinfection of the root canal with metronidazole and ciprofloxacin resulted in continued root maturation and thickening of root canal dentinal walls. 'Biologically-based procedures designed to replace damaged structures, including dentine and root structures, as well as cells of the pulp-dentine complex' are called regenerative endodontics (14). Regenerative endodontic therapy (RET) involves disinfection of the root canal system, provision of a scaffold, and introduction of stem cell activity followed by an adequate coronal seal (15). Recently, RET has been tried in cases of root resorption with considerable success. Regenerative or reparative endodontic treatment procedures may be an alternative approach to overcome the inherent problems of contemporary treatment of root resorption (16–18).

One literature review discussing the use of RET in teeth with internal root resorption concluded that it was a promising alternative to conventional root canal treatment (19). Another recent systematic review on external inflammatory lateral resorption in cases of post-traumatic tooth or pulp injuries inferred that RET may improve prognosis. However, only one database was searched in that review (20).

Hence, a thorough assessment of case reports, case series, and clinical studies utilising regenerative endodontics for treating different types of root resorption is necessary. This systematic review attempts to analyse the current clinical literature on this additional indication of RET as a treatment alternative for resorption cases.

MATERIALS AND METHODS

This systematic review used the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA 2020) statement guidelines (21). The protocol of this review was registered at PROSPERO (International prospective register of systematic reviews), bearing registration number CRD42021274569.

Search Strategy

A draft of the search strategy was developed based on key concepts about the topic.

Inclusion Criteria

All case reports, case series, and clinical studies describing the management of root resorption in mature or immature permanent teeth using RET. Relevant full-text articles in English published from 2001 [the year of publication of the first case of regeneration (13)] to September 2022 were included.

Exclusion Criteria

Case reports describing any other technique for management of root resorption, animal studies, RET in teeth showing no evidence of resorption, RET used for management of resorption

in deciduous teeth or teeth showing developmental anomalies & review articles were all excluded.

Using a database-appropriate syntax, search strategies were optimised for electronic databases MEDLINE, Scopus, Cochrane, and Google Scholar for relevant keywords, including MeSH terms (Table 1).

Also, manual screening of bibliographies of potentially eligible articles was done to identify any additional studies which could be included. A manual search of the Journal of Endodontics; International Endodontic Journal; Australian Endodontic Journal; Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology, and Endodontics; and Clinical Oral Investigations was performed.

Records from the searches were transferred to reference manager software Zotero 6.0.4 (Digital Software). Two authors (AD and KM) independently reviewed the title and the abstracts of all the articles selected to determine if the inclusion criteria were met. In case of disagreement, detailed discussions between all authors were conducted, and the senior reviewers' (NS and NV) decision was considered final (Fig. 1).

Data Extraction
Customised forms were used to extract the data from the selected studies (authors AD and AH) and verified independently by two authors (DS and NV). The data from the single non-randomised, single-arm, interventional was also tabulated under headings documenting the number and age of patients, cases selected, procedures employed, and conclusion of the study (Table 2) (22). For each of the case reports, and case series, the study characteristics extracted were author and year of publication, tooth number, patient age and sex, response to pulpal sensibility tests, root maturity, diagnosis, type of resorption, clinical steps in appointments, and outcomes (Table 3) (16, 18, 23–32). In case of any missing data in the manuscript, the authors were contacted through email to seek clarification.

Quality Assessment of Selected Studies
Only the first eight criteria out of the twelve components in the Methodological item for non-randomised studies (MINORS) tool (27) were used for the critical appraisal of the clinical study by Nageh et al. (22) since it was non-comparative (Table 4). The JBI Critical Appraisal Checklists were used to evaluate the quality of the selected case reports and case series (Tables 5, 6) (33, 34).

RESULTS

Out of the selected 19 full texts reviewed and analysed, 14 were selected. Among them, 1 was a clinical study (22), 1 was a case series (17), and 12 were case reports (Fig. 1) (16, 23–32).

The data from the articles showed that 34 teeth in 29 patients received RET for root resorption.

Demographics
The age of the patients treated was in the range of 7 to 28 years for the case reports, 9 to 12.5 years for the case series, and 13 to 30 years in the clinical study. Of the 29 patients, 11 were females, and 18 were males.

TABLE 1. Search strategy

Population: Patients having teeth with root resorption; Intervention: Regenerative Endodontic Therapy; Outcome: Arrest of resorption and healing

Database	Date of the last search	Filters applied	Results		
Medline	28.9.2022	Case Reports, Clinical Study, Clinical Trial, Randomized Controlled Trial, Humans, English	Search 1	(("root resorption"[Mesh]) OR ("tooth resorption"[Mesh])) OR ("*root resorption")	4875
			Search 2	((("Regenerative endodontics"[Mesh]) OR ("reparative endodontic")) OR (revascularisation)) OR (revitalisation)	12,015
			Search 1 and 2		33
Scopus	29.9.2022	Case Reports, Clinical Study, Clinical Trial, Randomized Controlled Trial, Humans, English	Search 1	(("root resorption"[Mesh]) OR ("tooth resorption"[Mesh])) OR ("*root resorption")	8278
			Search 2	((("Regenerative endodontics"[Mesh]) OR ("reparative endodontic")) OR (revascularisation)) OR (revitalisation)	1,13,278
			Search 1 and 2		43
Cochrane Central Library	28.9.2022	Trials	Search 1	("root resorption"):ti,ab,kw OR ("tooth resorption"):ti,ab,kw OR ("*root resorption"):ti,ab,kw	514
			Search 2	("regenerative endodontics"):ti,ab,kw OR ("reparative endodontics"):ti,ab,kw OR ("revascularization"):ti,ab,kw OR ("revitalization"):ti,ab,kw	12808
			Search 1 and 2		3
Google Scholar	29.9.2022	–	("*root resorption" OR "tooth resorption") AND ("regenerative endodontic" OR "revascularisation" OR "revitalisation" OR "reparative endodontic") AND (title:"case*" OR intitle:"clinical stud*" OR intitle: "*trial")		317

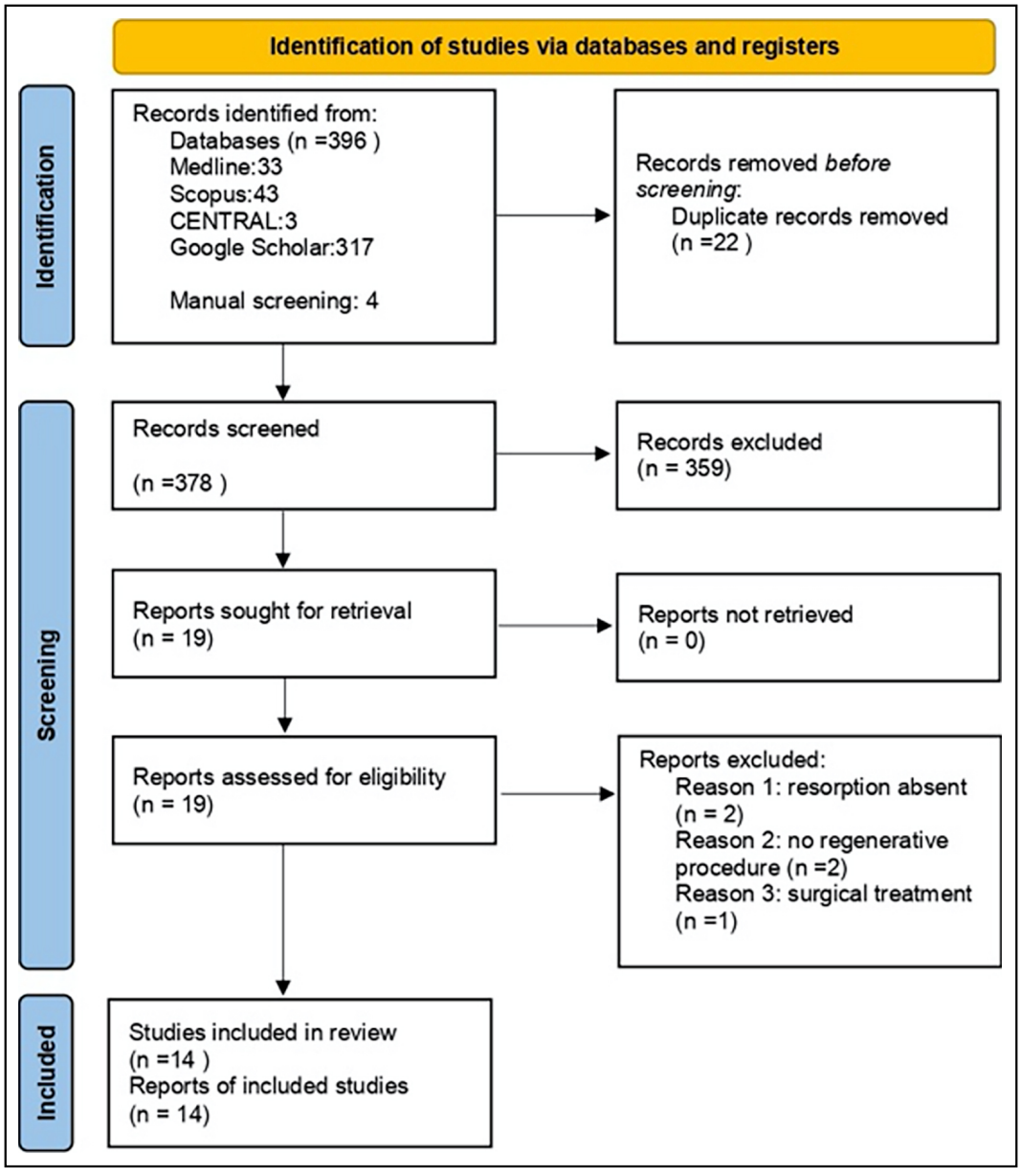

Figure 1. PRISMA flowchart

Tooth Type

All the cases documented in this review involve the anterior teeth (24 maxillary central incisors, 7 maxillary lateral incisors, 2 mandibular central incisors, 1 mandibular lateral incisors).

Response to Pulp Sensibility Tests

17 teeth mentioned in the case reports (16, 18, 23–30) and case series (17) responded negatively to pulpal sensibility testing before the RET, while 2 teeth responded positively (31, 32). In the clinical study, 3 teeth were vital, while 10 were necrotic (22). Post-treatment, 2 teeth in the case reports showed a positive response to pulp sensibility tests (25, 32). In 21 teeth, continued negative response was seen (16–18, 22, 29), while in the remaining cases (23, 24, 26–28, 30, 31), the authors did not mention the results of pulp testing after RET.

Maturity of Apex

24 of the 34 teeth treated had mature apices (16–18, 22–25, 29), while 10 teeth had immature apex (17, 18, 23, 26–28, 30–32).

History and Diagnosis

All the patients had a history of trauma ranging from crown fracture (n=3), crown fracture and avulsion (n=2), crown fracture and intrusion (n=1), and avulsion (n=8), crown fracture with intrusion and luxation (n=1); while 16 teeth had undesignated trauma. One case had a history of complicated crown fracture followed by a partial pulpotomy (31). In one case, the cause of root resorption was speculated as traumatic injury or a previous deep carious lesion (29), while in another, the history of trauma was not mentioned (16). Some periapical pathology was present in 30 of the 34 teeth included in the review.

Type of Resorption

Among the 16 teeth that had external inflammatory root resorption (13, 14, 17, 18, 20–22) (31, 32), 3 teeth had ankylosis (13), 1 tooth had ankylosis and replacement resorption (13) while 2 teeth had perforation (17, 22). 16 teeth had internal inflammatory root resorption (12, 16, 23) (30), out of which 2

TABLE 2. Summary of the clinical study by Nageh et al. (2021) (22) evaluating the management of internal inflammatory root resorption using injectable platelet-rich fibrin revascularisation technique

Number of patients	Age of patients (years)	Number of teeth	Cases selected	Method	Goals of treatment achieved	Conclusion
10	13–30	13 anterior mature teeth (7 maxillary central incisors, 4 maxillary lateral incisors, 1 mandibular central incisor, 1 mandibular lateral incisor)	All the patients had H/O trauma 8 patients (10 teeth) c/o mild to moderate dull pain on percussion and palpation tests with or without a fistulous tract, teeth discolouration, and IIRR with periapical radiolucency on the radiograph 2 patients (3 teeth) were asymptomatic, and routine radiographic examination IIRR. Type of resorption for all teeth: Internal inflammatory root resorption	First visit: RCO, BMP (size #40-80), 1.5% NaOCl irrigation with ultrasonic activation, CH, ICM, GIC seal After 2–4 weeks Second visit: irrigation 20 mL 17% EDTA, i-PRF in the canal covered with PRF membrane, White MTA+GIC+composite restoration	①Y ②P ③N	CBCT showed arrested lesions or progressively decreasing from their preoperative volumetric size, indicating repairing by mineralised-like deposits in the resorptive defects. The mean volume of IIRR lesions significantly decreased from (0.004±0.002 cm^3) preoperatively to (0.003±0.002 cm^3) postoperatively (p=0.011) Using i-PRF could arrest and allow for the healing of IIRR in permanent mature teeth and allows for periapical healing with successful clinical results

Sources of Funding for the study: Not reported. H/O: History of, c/o: Complaint of, IIRR: Internal inflammatory root resorption, RCO: Root canal opening, BMP: Biomechanical preparation, NaOCl: Sodium hypochlorite, CH: Calcium hydroxide, ICM: Intra canal medicament, GIC: Glass ionomer cement, EDTA: Ethylene diamine tetra acetic acid, i-PRF: Injectable platelet-rich fibrin, MTA: Mineral trioxide aggregate, ①: Primary goal, ②: Secondary goal, ③: Tertiary goal, Y: Yes; N: No; P: Partial fulfilment, CBCT: Cone beam computerised tomography

teeth also showed perforation (12, 23). Two teeth had both internal and external resorption (14, 19), out of which 1 had a perforation (Fig. 2) (14). No cases of cervical resorption were identified. Cone beam computed tomography (CBCT) was used for diagnosis in three case reports (16, 28, 29) and the clinical study (22), while intraoral periapical radiographs were used in the remaining cases.

Disinfection Protocol

Irrigation

For 33 teeth NaOCl was employed in varying concentrations ranging from 1–6% and different volumes ranging from 10–45 mL, respectively, as the primary irrigant. In one case, 2% chlorhexidine was used as an irrigant (32). Agitation of irrigant was achieved using ultrasonics in 16 teeth (22, 27–29) and negative pressure irrigation in one tooth (23). Sterile saline was used as an adjuvant in all cases. 17% ethylenediaminetetraacetic acid was used as a final irrigant in 28 teeth (16–18, 22, 23, 27–32).

Intracanal medicament

Among the cases covered under this review, 20 teeth used CH for durations ranging from 10 days to 3 months (16, 22, 23, 26–30). In 6 teeth, Triple antibiotic paste (TAP) [metronidazole, ciprofloxacin & minocycline in equal proportions] was employed for up to 1.5 months (18, 24, 32), while 3 teeth were treated with a mixture of metronidazole, cefuroxime axetil, and ciprofloxacin for 3 weeks (17). One tooth was treated with a double antibiotic paste (DAP) mixture using equal-weight ratios of metronidazole and ciprofloxacin (31). In the case reported by Harini et al. (2016) (25), the authors placed a watery slurry of metronidazole and minocycline (1:1) at the coronal level and sealed the tooth. 2 teeth in the cases reported by Yosphe et al. (2020) (17) and 1 tooth in the case report by Saoud et al. (2016) (18) were given both CH and TAP as intracanal medicament. CH was placed for the first 2–4 weeks and TAP for 2–3 weeks subsequently.

Formation of a blood clot

After disinfection of the canal and resolution of symptoms, bleeding was induced in 14 teeth (16, 18, 23, 24, 26–30, 32). Instruments like K or Hedström files were used beyond the apex (range reported 2–3 mm) to form the blood clot. In one case MicroOpener was used to provoke bleeding inside the resorption cavity (29).

Use of autologous plasma concentrates (APCs)

The canal was filled with platelet-rich plasma (PRP) in 1 tooth, (25) platelet-rich fibrin (PRF) in 5 teeth (17), or a combination of injectable PRF (iPRF) and PRF in 13 teeth (22).

In one case, bleeding was induced using a 30# K file and the clot was covered with PRF (31).

Coronal plug

Mineral trioxide aggregate (MTA) was used as the coronal plug in 28 teeth (16, 18, 22–24, 26–32), while 5 teeth utilised a combination of collagen plug and Biodentine (17). A glass ionomer cement seal was placed directly in one tooth (25).

TABLE 3. Data extraction table for Case series and Case reports

Case series

Author	Tooth number	Age/ gender	History and diagnosis	Type of resorption	Clinical steps		Goals of treatment achieved	Follow up
					First appointment	Second/third appointments		
Yosphe et al. (2020) (17) n=5	Case 1: 11 (M), 21 (M)†	12/ male	H/O of dental trauma 11, 21: necrotic pulp with symptomatic apical periodontitis	EIRR+ Ankylosis	• Irrigation with 20 mL 1.5% NaOCl • TAP ICM (metronidazole + cefuroxime axetil+ciprofloxacin) • Seal IRM	After 3 weeks • A final rinse with 17% EDTA • PRF was inserted up to the level of the cementoenamel junction. • Resorbable Collagen Plug+ Biodentine • Sealed with GIC	①Y ②P ③N	30 months Percussion testing did not reveal any metallic sound in either tooth that was noted preoperatively.
	Case 2: 11 (IM)	11.5/ male	H/O Avulsion, class III fracture necrotic pulp with symptomatic apical periodontitis	EIRR + Replacement resorption (ankylosis)	Case 2 & 3: CH ICM for 4 weeks before TAP		①Y ②Y ③N	22 months. Percussion testing did not reveal any metallic sound that was noted preoperatively.
	Case 3: 21 (M)†	12.5/ female	H/O Avulsion necrotic pulp with chronic apical abscess	EIRR			①Y ②P ③N	24 months.
	Case 4: 11 (IM)	9/ female	H/O Avulsion, Class IV crown fracture Necrotic pulp with asymptomatic apical periodontitis	EIRR + Ankylosis			①Y ②N† ③N	12 months. The ankylotic sound persisted, with no change in occlusal level. Inflammatory resorption was arrested, followed by replacement resorption.

Case reports

Author	Tooth number	Age/ gender	Diagnosis	Type of resorption	Clinical steps		Goals of treatment achieved	Follow up
					First appointment	Second/third appointments		
Miller et al. (2012) (32) n=1	21 (IM)	9/ male	H/o Avulsion asymptomatic irreversible pulpitis with asymptomatic apical periodontitis	EIRR†	• Irrigation with 2%CHX + 17%EDTA • TAP ICM • Fuji triage seal	• After 2 weeks • • CH replaced • • Third appointment: • 6 weeks after the initial appointment	①Y ②Y ③Y	13 months, Internal bleaching at 24 weeks to remove the cervical discolouration
Chaniotis A (2015) n=1	31 (IM)	7/ female	H/O Avulsion pulp necrosis and asymptomatic apical periodontitis	EIRR with perforation	• CH in access cavity • Cavit G Temporary • (Uncooperative patient)	• • ultrasonically activated 3% NaO After 2 weeks • CH replaced	①Y ②Y ③NR	2 years, MTA-induced cervical discolouration seen

TABLE 3. Cont.

Case reports

Author	Tooth number	Age/ gender	Diagnosis	Type of resorption	Clinical steps		Goals of treatment achieved	Follow up
					First appointment	Second/third appointments		
						• pressure irrigation, followed by 10 mL of 17% EDTA solution • Canal flooded with 17% EDTA solution for 5 min, followed by a final rinse of sterile water • Bleeding was induced using a 25 K file to probe periapical tissue • After clotting, the white MTA plug • Dual cure composite resin restoration		
Santiago et al. (2015) (24) n=4	Case 1: 11 (M), 21 (M)	9/ male	H/O uncomplicated crown fracture 11: pulp necrosis, chronic apical abscess. 21: pulp necrosis, asymptomatic apical periodontitis	11: EIRR (advanced) 21: EIRR.	• Irrigation with 20 mL 5.25% NaOCl followed by 10 mL sterile saline solution • TAP ICM • GIC seal	After 30 days • Irrigation with 20 mL 5.25% NaOCl followed by 10 mL sterile saline solution • Bleeding evoked using a K file 2 mm beyond the apex • After the formation of a blood clot seal of MTA + GIC + composite resin	①Y ②NA ③NR	21 developed new periapical radiolucency at the 27-month appointment At 30 months conventional root canal treatment was performed for 21 teeth, with crown discolouration with 11.
	Case 2: 21 (M)	9/ male	H/O Avulsion pulp necrosis, symptomatic apical periodontitis ()	EIRR (advanced)			①Y ②NA ③No	18 months, crown discolouration
	Case 3: 11(M)	8/ male	H/O Avulsion 11, 21: pulp necrosis, asymptomatic apical periodontitis	11: EIRR (early)			①Y ②NA ③NR	15 months, crown discolouration
Saoud et al. (2016) (18) (Case 1: unrelated to current SR) n=2	Case 2: 21 (IM)	7/ female	H/O Avulsion pulp necrosis, symptomatic apical periodontitis	†EIRR (as seen on radiograph)	• Minimal filing and irrigation with 1% NaOCl. • TAP ICM • Seal with Cavit, GIC	• After 4 weeks • Irrigation with 17% EDTA • Bleeding induced using size 25 K-file 2 mm beyond apex • Seal with MTA + light-cured composite resin	①Y ②Y ③N	5-year. Recurrent trauma led to mid-root horizontal root fracture requiring splinting. 6 weeks after, the root fracture showed deposition of calcific tissue formation and connective tissue healing.

TABLE 3. Cont.

Case reports

Author	Tooth number	Age/ gender	Diagnosis	Type of resorption	Clinical steps		Goals of treatment achieved	Follow up
					First appointment	Second/third appointments		
	Case 3: 11 (M)	16 / male	H/O uncomplicated crown fracture Pulp necrosis, acute apical abscess	IRR and External root resorption with perforation	• Irrigation with 2.5% NaOCl • Debridement up to #30 K-files till WL • Internal root • Resorptive area debrided with a size 2 GG with a 1-mm tip removed • Metapaste ICM • IRM seal	• After 2 weeks • Irrigation with 2.5% NaOCl • Seepage of straw-coloured fluid present • The resorptive area was debrided with a size 2 GG with a 1-mm tip removed • TAP ICM, IRM seal Third appointment: • After 2 weeks • Irrigation with 2.5% NaOCl, sterile saline, and final flush of 17%EDTA • Bleeding induced using size 20 K-file 2-3 mm into periapical tissue • After approximately • After 10 to 15 minutes, MTA plug • Seal with IRM and later, LCC	①Y ②P ③N	19 months
Harini et al. (2016) (25) n=1	21 (M)	11/ male	H/O Avulsion Pulp necrosis	IRR and External root resorption (After replantation of PRP-filled teeth)	• Preparation of avulsed tooth: pulp extirpation, irrigation with normal saline and 5.25% NaOCl, root apex was enlarged to 1.5–2 mm, soaked in doxycycline solution for 15 to 20 minutes. • Replantation, splinting • PRP injected • Seal with GIC.	After 6 months • Dislodged coronal GIC removed • Metronidazole + minocycline slurry inserted into the root canal at CEJ level with a syringe • Sealed with GIC, crown restored with composite	①Y ②NA ③N	12-month
Dastpak et al. (2017) (26) n=1	22 (IM)	24/ female	H/O Trauma Acute exacerbation of asymptomatic apical periodontitis	EIRR	• Irrigation with 5.25 % NaOCl for 5 minutes, followed by irrigation with 10 mL saline • CH ICM • Seal with Cavit	After 3 weeks • Irrigation with 5.25% NaOCl + 10 mL saline solution. • Bleeding evoked using a K- file beyond the root apex. • MTA and a temporary restoration • Third appointment: • After 1 week, seal with a composite restoration	①Y ②Y ③NR	12 months. After 12 months, the patient was referred to the restorative department to repair the crown discolouration.

TABLE 3. Cont.

Case reports

Author	Tooth number	Age/ gender	Diagnosis	Type of resorption	Clinical steps		Goals of treatment achieved	Follow up
					First appointment	Second/third appointments		
Kaval et al. (2018) (16) n=1	22 (M)	14/ female	H/O trauma not mentioned Symptomatic apical periodontitis	Perforated IRR (4.6×4.5× 3.8 mm)	• Coronal to IRR, BMP up to size 80 K-file • The apical part of the root canal is prepared up to a size 45 K-file • Irrigation with 1% NaOCl, distilled water • Final flush 17% EDTA • ICM CH paste • Seal with GIC	• Seal with GIC • Third appointment: • After 3 months • Irrigation with 1% NaOCl, 17% EDTA, and distilled water • Bleeding induced with size 20 K-file into periapical space • CH paste placed • After the formation of a blood clot MTA + GIC • GIC later replaced by composite resin	①Y ②NA ③N CBCT used	2 years (1.1 × 1.5 mm hard tissue formation was apparent between the coronal and root pulp tissues)
Tzanetakis GN (2018) (27) n=1	21 (IM)	7/ male	H/O uncomplicated crown fracture and intrusive luxation Acute alveolar abscess	EIRR	• Irrigation with • 10 mL 1% NaOCl • Ultrasonic activation of NaOCl for 60 seconds • Irrigation with 10 mL 1% NaOCl • ICM CH paste • Seal with Cavit G	After 2 weeks • Irrigation with 5 mL 1% NaOCl, ultrasonic activation of NaOCl for 30 seconds • Final rinse with 10 mL 17% EDTA • Bleeding induced with #60 Hedstrom 2mm beyond apex • ProRoot MTA condensed in the coronal third of the canal Third appointment: After 3 days • MTA setting confirmed • Seal of GIC+light-cured composite	①Y ②P ③NR	30 months
Lu et al. (2020) (28) n=1	21 (IM)	9/ female	H/O Avulsion Necrotic pulp and symptomatic apical periodontitis	EIRR with perforation	#First Appointment • Irrigation with 1.5% NaOCl • Ultrasonic activation was performed for 60 seconds • CH ICM • GIC seal	After 2 weeks • Irrigation with 1.5% NaOCl and saline • A final rinse with 17% EDTA • Bleeding was induced using a #25 sterile K-file 2 mm beyond the apex • CollaCote + 3 mm MTA • Seal with GIC and composite resin	①Y ②p ③N CBCT used	30 months

TABLE 3. Cont.

Case reports

Author	Tooth number	Age/ gender	Diagnosis	Type of resorption	Clinical steps		Goals of treatment achieved	Follow up
					First appointment	Second/third appointments		
Arnold M (2021) (29) n=1	22 (M)	28/ male	H/O trauma/deep caries? pulp necrosis with chronic apical abscess	Perforating internal inflammatory resorption	• Removal of necrotic tissue above the area of resorption • Ultrasonically activated 3% NaOCl • ICM CH mixed with saline for 2 weeks	Third appointment: 6 weeks after the initial appointment • Ultrasonically activated 3% NaOCl • 1-minute rinse with 17%EDTA • Bleeding provoked inside the resorption cavity using the MicroOpener • After 10 minutes, the bleeding stopped MTA+composite	①Y ②NA ③N CBCT used	3 years
Chitsaz et al. (2021) (31) n=1	21 (IM)	8/ female	H/O complicated crown fracture followed by partial pulpotomy Irreversible pulpitis with symptomatic apical periodontitis†	EIRR	• WL established • 1.5% NaOCl irrigation • Gentle mechanical instrumentation. • DAP (equal wt. ratios of metronidazole and ciprofloxacin) ICM • Sealed reinforced zinc oxide eugenol cement	After 3 weeks • ICM removed with 20 mL normal saline • Irrigation with 20 mL of 17% EDTA solution for 5 min. • Bleeding induced using #30 K-file beyond the apex • PRF placed within the coronal part of the root canal • The light-cured dentine bonding agent applied to the labial surface of the pulp chamber • MTA+reinforced zinc oxide eugenol cement • Third Appointment After four days • Coronal restoration: light cure GIC+Filtek Z350	①Y ②P ③NR	10 months, evidence of tooth discolouration
Loroño G et al. (2022) (30) n=1	21(IM)	8/ male	Pulp necrosis and chronic apical abscess (H/O intrusion-injury, severe luxation, uncomplicated crown fracture)	Internal root resorption	• WL established • No Instrumentation • Gentle irrigation with 20 mL 1.5% NaOCl, saline • Final irrigation with 20 mL of 17% EDTA • Canal dried and CH ICM • Temporary Cavit G	After 3 weeks • Irrigation with 20 mL of 17% EDTA for 5 minutes • Canal dried • Bleeding induced with #30 K-File 3 mm beyond the apex • Collagen sponge+ white MTA • Temporary Cavit G Third Appointment After 3 days • Cavity sealed with GIC + LCC	①Y ②P ③NR	54 months

Preoperatively, all the teeth in the above table responded negatively to pulp sensibility testing. Sources of Funding for the above studies: Not reported. †: As judged by authors, #: Steps after local anaesthesia was administered and access opening. H/O: History of, ①:Primary goal, ②: Secondary goal, ③: Tertiary goal, EIRR: External inflammatory root resorption, IRR: Internal root resorption, RCO: Root canal opening, TAP:Triple antibiotic paste, IRM: Intermediate restorative material, GIC: Glass ionomer cement, EDTA: Ethylene diamine tetra acetic acid, CH: Calcium hydroxide, NaOCl: Sodium hypochlorite, ICM: Intracanal medicament, MTA: Mineral trioxide aggregate, RCT: Root canal treatment, GG: Gates glidden, WL: Working length, SR: Systematic review, LCC: Light cured composite, PRP: Platelet-rich plasma, PRF: Platelet-rich fibrin, Y: Yes; N: No; P: Partial fulfilment; NA: Not applicable; NR: Not reported, M: Mature apex, IM: Immature apex, CBCT: Cone beam computed tomography

TABLE 4. Critical appraisal of the clinical study by Nageh et al. (22) using the MINORS tool

The Methodological item for the non-randomized studies (MINORS) tool	
Major Components	**Response options**
1. A clearly stated aim	Reported and adequate (2 points)
2. Inclusion of consecutive patients	Reported and adequate (2 points)
3. Prospective collection of data	Reported and adequate (2 points)
4. Endpoints appropriate to the aim of the study	Reported and adequate (2 points)
5. Unbiased assessment of the study endpoint	Reported and adequate (2 points)
6. Follow-up period appropriate to the aim of the study	Reported and adequate (2 points)
7. Loss to follow of less than 5%	Reported and adequate (2 points)
8. Prospective calculation of the study size	Reported and adequate (2 points)
Total score	16

TABLE 5. JBI critical appraisal for case series

Article	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Overall appraisal	Score (out of 10)	Quality
Yosphe et al. (2020) (17)	N	Y	Y	UN	UN	Y	N	UN	N	NA	I	3	Poor

JBI: Joanna Briggs Institute, Q1: Were there clear criteria for inclusion in the case series?, Q2: Was the condition measured in a standard, reliable way for all participants in the case series?, Q3: Were valid methods used to identify the condition for all participants included in the case series?, Q4: Did the case series have consecutive inclusion of participants?; Q5: Did the case series have complete inclusion of participants?, Q6: Was there clear reporting of the participants' demographics in the study?, Q7: Was there clear reporting of clinical information of the participants?, Q8: Were the outcomes or follow-up results of cases reported?, Q9: Was there clear reporting of the presenting site(s)/clinic(s) demographic information?, Q10: Was statistical analysis appropriate?, Y: Yes, N: No, UN: Unclear, NA: Not applicable, I: Include, E: Exclude, Quality rating: poor 0-3; fair 4–7; good 8–10

TABLE 6. JBI critical appraisal for case reports

Point	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Overall appraisal	Score (out of 8)	Quality
Article											
Miller et al. (2012) (32)	Y	Y	Y	Y	Y	Y	Y	Y	I	8	Good
Chaniotis A (2015) (23)	Y	Y	Y	Y	Y	Y	Y	Y	I	8	Good
Santiago et al. (2015) (24)	Y	Y	Y	Y	Y	Y	Y	Y	I	8	Good
Saoud et al. (2016) (18)	Y	Y	Y	Y	Y	Y	Y	Y	I	8	Good
Harini et al. (2016) (25)	Y	Y	Y	Y	Y	Y	U	Y	I	7	Good
Dastpak et al. (2017) (26)	Y	Y	Y	Y	N	N	Y	N	I	5	Fair
Kaval et al. (2018) (16)	Y	N	Y	Y	Y	Y	U	Y	I	6	Good
Tzanetakis GN (2018) (27)	Y	Y	Y	Y	Y	Y	U	Y	I	7	Good
Lu et al.(2020) (28)	Y	Y	Y	Y	Y	Y	U	Y	I	7	Good
Arnold M (2021) (29)	Y	Y	Y	Y	Y	Y	U	Y	I	7	Good
Chitsaz et al., 2021 (31)	Y	Y	Y	Y	Y	Y	Y	Y	I	8	
Loroño G et al. (2022) (30)	Y	Y	Y	Y	Y	Y	Y	Y	I	8	Good

JBI: Joanna Briggs Institute, Q1: Were the patient's demographic characteristics clearly described?, Q2: Was the patient's history clearly described and presented as a timeline?, Q3: Was the patient's current clinical condition on presentation clearly described?, Q4: Were diagnostic tests or methods and the results clearly described?, Q5: Was the intervention(s) or treatment procedure(s) clearly described?, Q6: Was the post-intervention clinical condition clearly described?, Q7: Were adverse events (harms) or unanticipated events identified and described?, Q8: Does the case report provide takeaway lessons?, Y: Yes, N: No, U: Unclear, I: Include, E: Exclude, S: Seek further information, Quality rating: poor 0–2; fair 3–5; good: 6–8

Outcomes

The follow-up period after RET ranged from 10 months to 5 years (average 20.3 months). The success of RET depends on the extent to which primary, secondary, and tertiary goals are achieved.

- Primary goal: Elimination of symptoms and evidence of bony healing.
- Secondary goal: Increased root wall thickness or increased root length
- Tertiary goal: Positive response to vitality testing (35).

RET was essentially used as a root resorption treatment in the cases reported here. Hence, the primary aim of the treatment was also the arrest of root resorption. All the cases reported in the included studies achieved their primary goal because the patients were asymptomatic, arrest of root resorption was seen, and the tooth remained stable and functional after RET. In cases where a periapical lesion was present, healing was evident for all cases. Among the 10 immature teeth, secondary

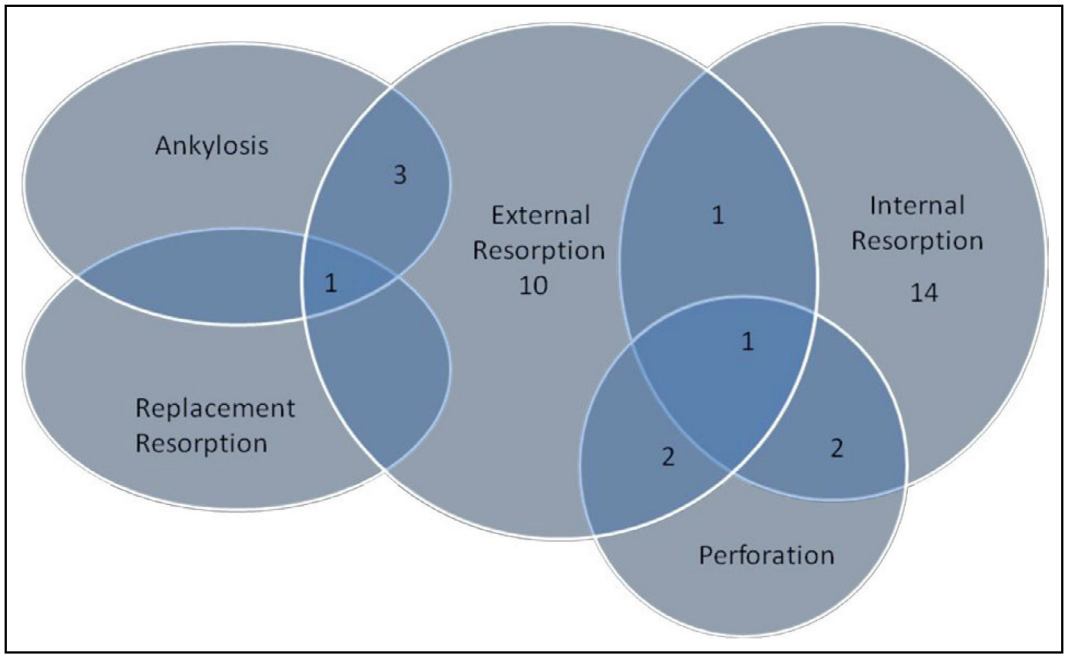

Figure 2. Venn Diagram showing types of resorptions present in the cases under study

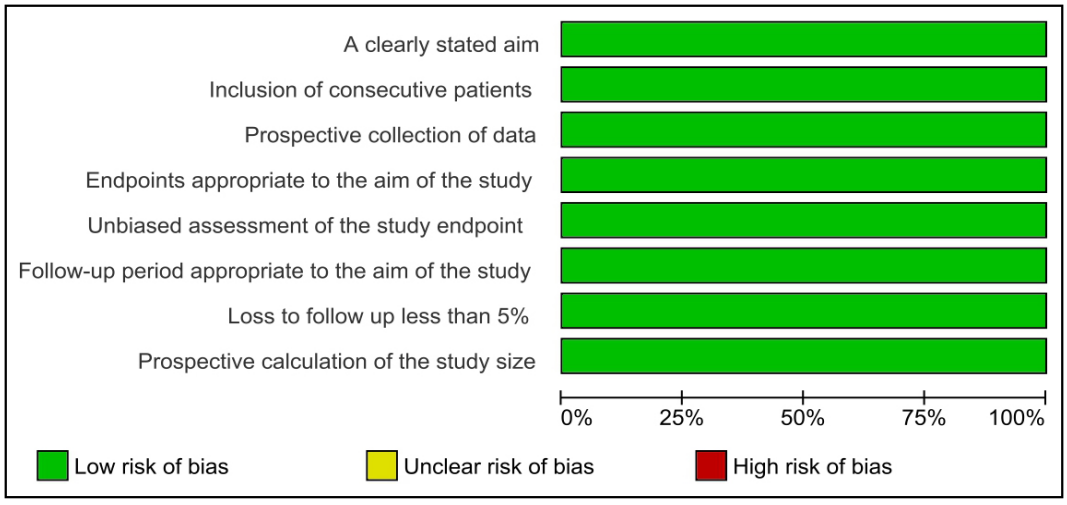

Figure 3. MINORS-risk of bias graph

MINORS: Methodological item for non-randomised studies

goals were achieved in 5 teeth (17, 18, 23, 26, 32) and partial in 4 teeth (27, 28, 30, 31). In one tooth, replacement resorption set in after inflammatory resorption was arrested (17). However, one mature left maxillary central incisor developed new periapical radiolucency at the 27-month follow-up appointment. For the thirteen teeth in the Nageh et al. (22) clinical study, the CBCT imaging readings of internal inflammatory root resorption and periapical lesions revealed a significant volumetric decrease (p=0.00) at the end of the 12-month follow-up period, thus quantitatively documenting the attainment of primary and secondary goals of RET.

Quality Analysis

The clinical study by Nageh et al. (22) obtained the global ideal score of 16 for non-comparative studies using the MINORS scale and was deemed good quality (Figs. 3, 4). This study utilised uniform treatment modalities and presented the possibility of quantitative evaluation of the outcome of RET in internal root resorption. The JBI critical appraisal tool, when applied to the case series by Yosphe et al. (2020) (17), showed that it was of poor quality (Figs. 5, 6). The JBI critical appraisal tool showed that eleven of the case reports (16, 18, 23–25, 27–32) were of good quality, while one case report (26) was of fair quality (Figs. 7, 8).

DISCUSSION

The current study attempted to systematically review all clinical cases of root resorption treated with RET. To the authors' knowledge, this is the first systematic review summarising all the available clinical evidence on the effectiveness of RET in all types of root resorption. Unfortunately, a meta-analysis could not be conducted as the data available was heterogeneous.

RET techniques may offer a chance to replace the damaged pulp and tooth structure with vital tissues that serve as a defen-

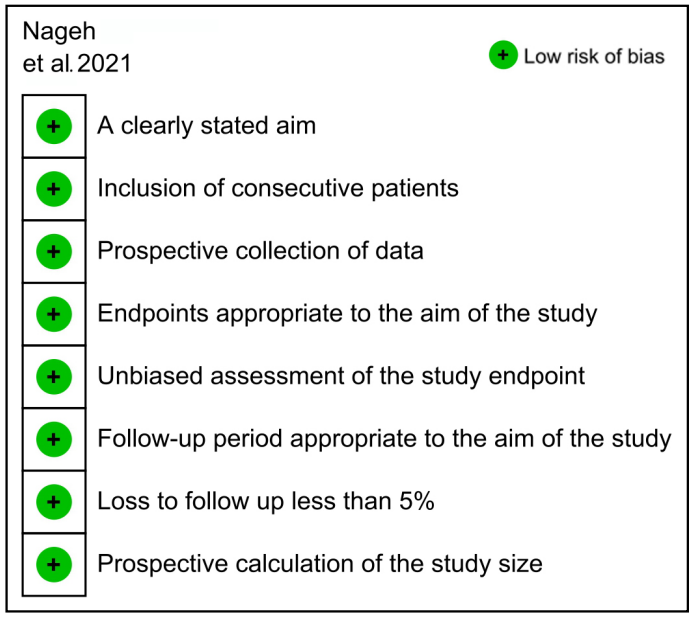

Figure 4. MINORS-risk of bias summary

MINORS: Methodological item for non-randomised studies

sive mechanism during tissue injury or microbial assault and reduce the probability of tooth fracture (22). Studies investigating the histologic nature of the tissues growing into the root canal space after RET in mature and immature have documented the presence of connective tissue with structures resembling bone and cementum (36, 37). The cementum-like tissues formed in the root canal space after RET may contain an inhibitor of osteoclastogenesis resulting in the arrest of root resorption (4, 15). Also, it has been speculated that the vital tissue in the canal may prevent progressive replacement resorption (28).

The success of RET may be affected by various factors like age, maturity of the apex and apical diameter (38–40), microbial control procedures (41), and the creation of a blood clot or protein scaffold in the canal (42, 43).

In the studies included in our review, when RET was used for resorption, the outcomes did not seem to be affected by the patient's age and the tooth's maturity. These findings align with a study by Arslan et al. (2019) (44), who concluded that age had no significant effect on the healing size of the radiographic lesion following RET. Also, one systematic review by Scelza et al. (2021) (45) reported that the calculated levels of RET success in mature teeth were similar to those reported for immature teeth. The wide area of communication with the surrounding periodontal ligament space due to resorption may have facilitated the ingrowth of blood vessels in five mature teeth cases included in this review (12, 14, 17, 22, 23).

It was noted that varied protocols for microbial control procedures that allow for stem cell survival had been used to manage resorption cases with RET. Due to the irregular nature of the resorptive defect, NaOCl is the irrigant of choice to dissolve pulp tissue remnants and enhance disinfection. The AAE guidelines recommends low concentrations of NaOCl [1.5–3%] (35). The higher concentrations of NaOCl [5.25–6%] used in seven teeth (23–26) and 2% chlorhexidine in one tooth (32) may be potential causes of stem cell damage (46). In the case of internal resorptions, the use of agitation may facilitate penetration of the irrigant into the resorptive defects, thus improving chemical disinfection and removal of granulation tissue, organic debris, and biofilms (22).

Six teeth in the selected studies did not follow the AAE protocol of final rinse with EDTA. EDTA facilitates the removal of the smear layer resulting in better penetration of intracanal medicaments. It also helps release growth factors from dentine, facilitates the inductive properties of dentine-derived morphogens, and positively affects stem cells' survival, differentiation, and attachment (41). This may consequently facilitate the formation of new tissue and the arrest of resorption. Lastly, it may also help reverse the detrimental effects of NaOCl if used as a final wash (41).

Traditionally, long-term CH has been utilised as an intracanal medicament in the preventive and interceptive management of resorption in avulsed, replanted, mature teeth (47). CH is effective as an antimicrobial intracanal medicament during RET and allows for the survival and proliferation of the stem cells of the apical papilla (15, 48). The arrest of root resorption by CH is

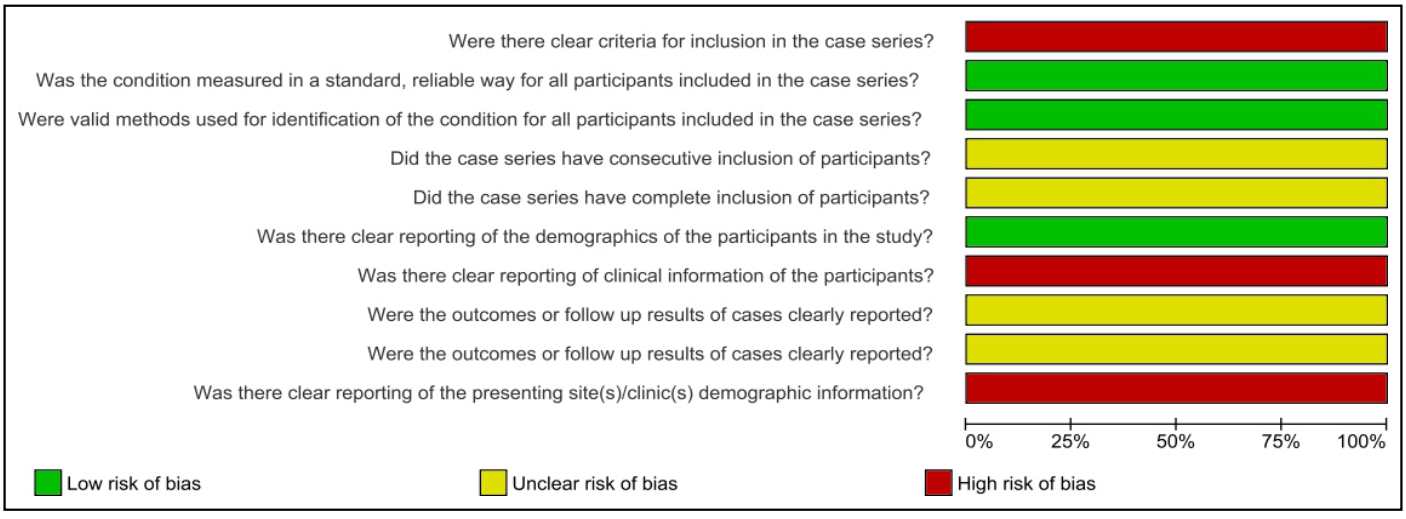

Figure 5. Case series-risk of bias graph

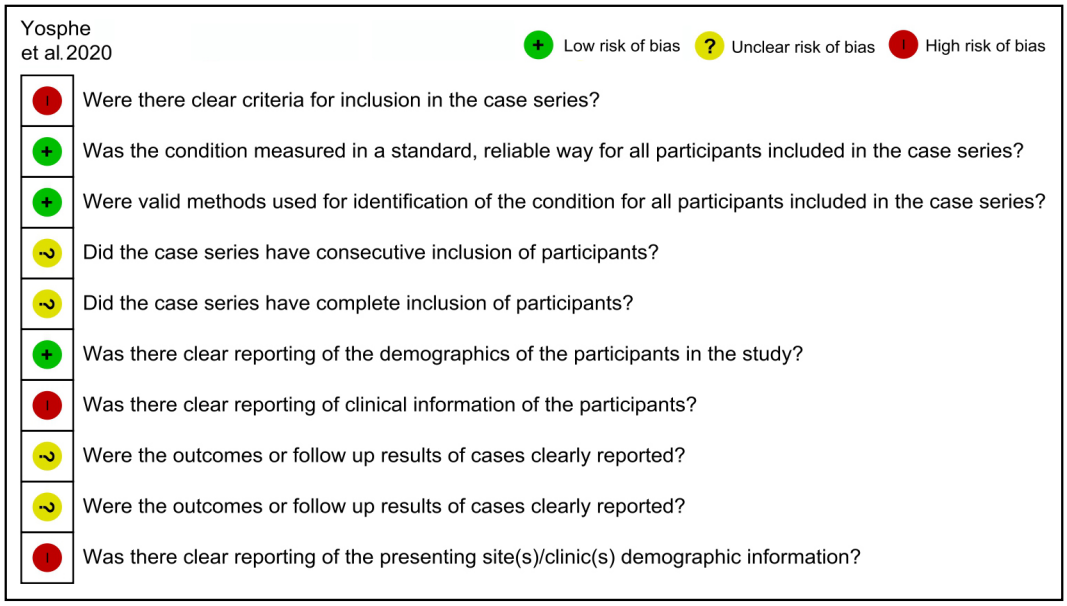

Figure 6. Case series–risk of bias summary

attributed to its antibacterial potential as well as its alkalising effect, which activates alkaline phosphatase and impedes osteoclastic activity (49). The use of TAP to combat endodontic infections was first suggested by Hoshino et al. (1996) (50). While it also has antibacterial action, another possible hypothesis to explain the arrest of root resorption after its use may be the immunomodulatory effect of ciprofloxacin and metronidazole on the RANK-RANKL-OPG system responsible for root resorption (4). While TAP and CH are equally effective as disinfectants in regenerative procedures, the latter may be used to avoid dental discolouration caused by tetracyclines (39). Lower concentrations (0.01–0.1 mg/mL) are recommended to prevent a negative effect on stem cells (31). Although the procedure for making TAP has been documented in the cases reviewed here, the final concentration has not been reported in any of the included articles. Alternatively, CH may be first used, followed by TAP if the treatment dictates more aggressive disinfection (41).

After disinfection of the canal and resolution of symptoms, induction of a blood clot or introduction of autologous platelet concentrates (APC) was done in the canal. However, a study by Harini et al. (2016) (25) followed a regenerative protocol that differed considerably from the one recommended by AAE. In this case, replanted avulsed mature tooth was filled with PRF. However, after resorption areas developed, DAP was placed in the access cavity and sealed.

Bleeding was evoked by using a K or H-file beyond the apical foramen to fill the canal with blood to the level of the cementoenamel junction in 14 teeth. This procedure triggers a significant accumulation of undifferentiated stem cells in the canal space (48). Alternatively, APCs like platelet-rich plasma (PRP), platelet-rich fibrin (PRF), or injectable platelet-rich fibrin (iPRF) have been used in 19 teeth among the studies included in this review. These release growth factors and cytokines that modulate stem cell proliferation and differentiation, extracellular matrix synthesis, chemotaxis, and angiogenesis, thus facilitating regeneration (42). Additionally, PRF has been shown to upregulate the OPG-to-RANKL ratio, which promotes mineralisation (51). iPRF may provide an added advantage of flowing in irregular resorptive cavities and inaccessible areas owing to its liquid form (22).

The outcomes of the cases reported in the included studies have been categorised on the extent to which primary, secondary, and tertiary goals were achieved (Table 3) (35). Despite the varied disinfection protocols used in the studies included in this review, RET successfully arrested root resorption in all the cases. However, in one mature left maxillary central incisor, although an initial revascularisation process was reported, a new periapical radiolucency developed at the 27-month follow-up (24). Possible causes for this negative outcome may be related to the use of high NaOCl concentration (without agitation) and the lack of a final rinse of 17% EDTA. The authors of the study have not mentioned the concentration of TAP used. Although insignificant, the tooth's mature apex may also be a contributory factor. However, since the adjacent tooth treated with a similar clinical protocol had a successful outcome, a local cause like loss of coronal seal cannot be ruled out.

Achievement of the secondary goal, which includes thickening of dentinal walls, is essential in cases of internal resorption where core dentine is resorbed. 2 teeth in the case report (18, 29) and 13 teeth in the clinical study (22) showed RET leading to the deposition of hard tissue in the resorptive areas and dentinal walls that would reinforce the weakened walls.

A positive response to pulpal vitality testing is considered to be indicative of highly successful treatment and is the tertiary goal of RET. It may indicate the return of the neural capacity and hence a better-organised pulp tissue (35, 48). However, the teeth may be unresponsive to sensibility testing after RET due to the thickness of the MTA layer and its position below the enamel–dentine junction (52). Another effect of the coronal MTA in immature teeth may be the inadvertent failure of root canal walls to thicken at the cervical area (15). This may, in turn, make the tooth susceptible to fracture. Indeed, in one of the cases, re-

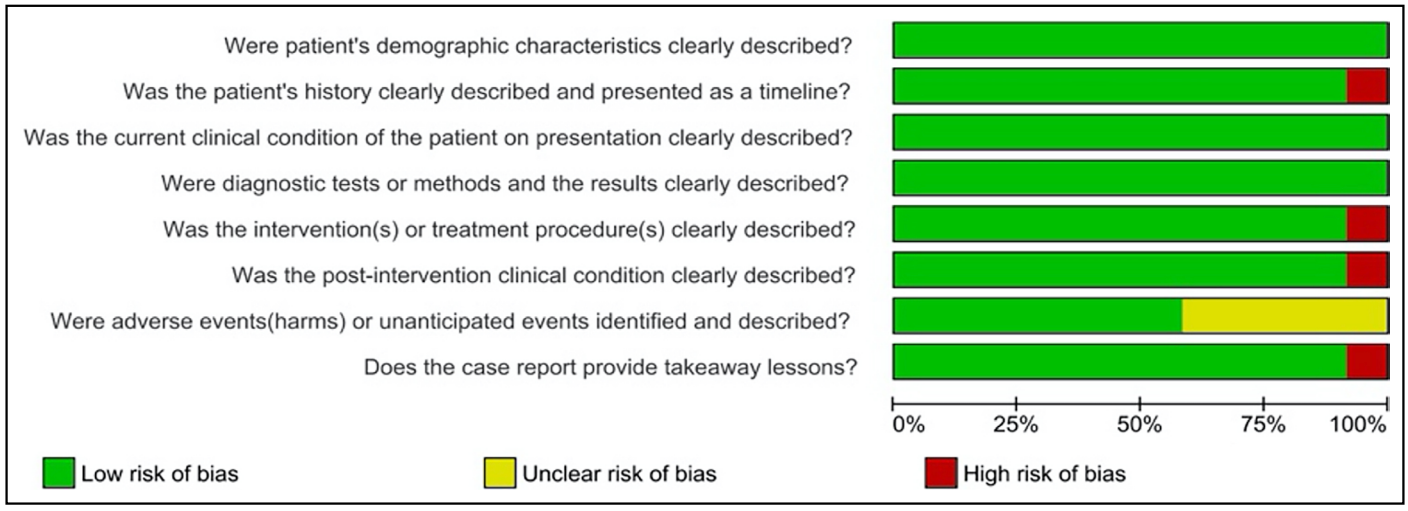

Figure 7. Case reports-risk of bias graph

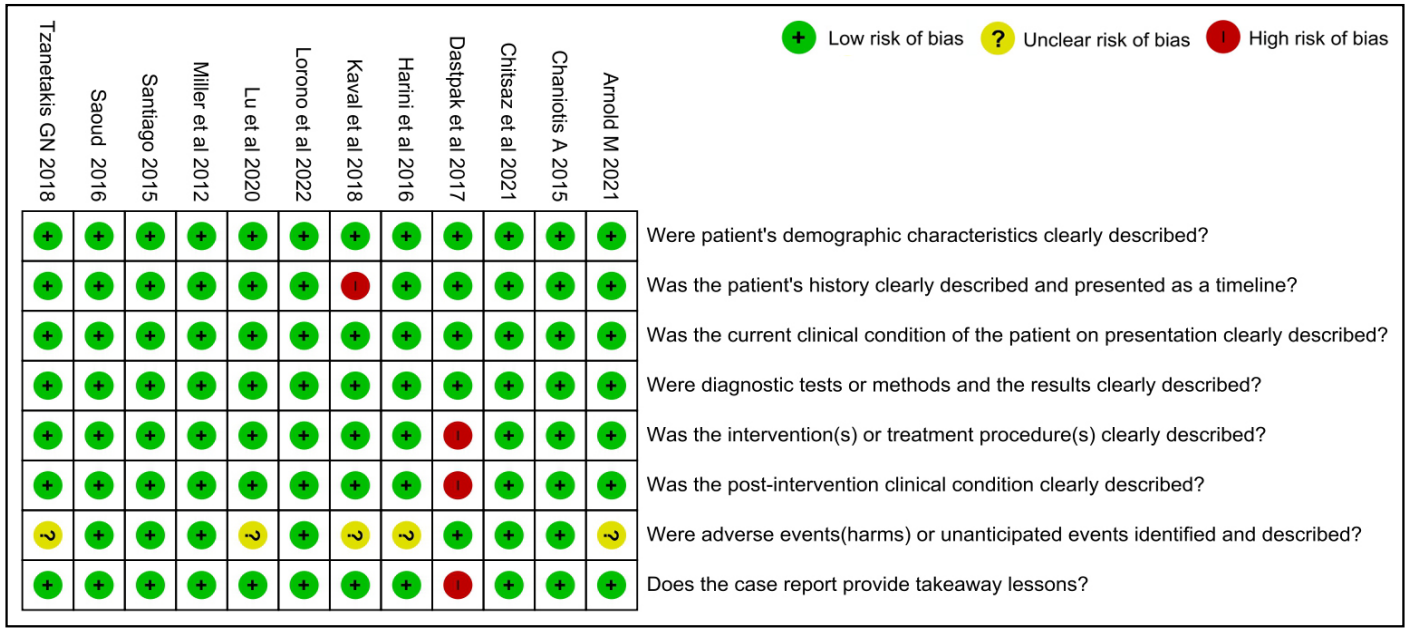

Figure 8. Case reports-risk of bias summary

current trauma led to a mid-root horizontal root fracture in the tooth previously treated for resorption using RET (18).

In all the case reports and case series included here, assessing the degree of resorption preoperatively and postoperatively was subjective. A high-resolution, small field of view, CBCT may afford increased detection and accurate determination of the extent and nature of root resorption lesions (2). In the clinical study by Nageh et al., (22) the precise volumetric reduction in the resorption areas before and after the intervention has been documented using CBCT. As with RET cases (15), publication bias may be possible as it is likely that only the cases successful in managing resorption are being submitted for publication. Also, the long-term prognosis of RET still needs to be fully understood. It may be associated with complications, such as ankylosis, calcification, obliteration, tooth fracture, periapical tissue inflammation, or lack of further root growth (46). In cases of severe root resorption, revascularisation-associated intracanal calcification may help compensate for lost tooth tissue. However, it may lead to the complete obliteration of the root canal and impede the normal function of the pulp (53). All the currently available data on the use of RET in teeth with resorption is limited to only anterior teeth, and all the cases were managed non-surgically. Previous literature also confirms that root resorption secondary to trauma is most frequently seen in incisors (54). Also, its effectiveness in arresting resorption triggered by causes other than trauma like caries or periodontal infections has not been investigated. However, no correlation between the success of RET and the aetiology of pulp necrosis has been established (55, 56).

Case reports and series form a considerable amount of the published literature on using RET to manage root resorption. This can be considered the major limitation of this review.

Our findings agree with the earlier two reviews by Ashraf & Alfayate (19) and Lin et al. (20), who concluded that RET might be considered a choice for treating cases of internal root re-

sorption and external lateral inflammatory resorption, respectively. However, all the different types of resorptions except cervical resorption that were managed using RET were analysed systematically in this article. This can be considered the major strength of this review. RET may currently be the only treatment available for replacement resorption and cases of root resorption where the prognosis is guarded. Future clinical studies using uniform clinical protocols for RET in resorption cases are needed to establish a better quality of evidence. Further, the management of resorption defects using innovations in regenerative dentistry like encapsulated human umbilical cord mesenchymal stem cells in a plasma-derived biomaterial (57), circulating blood (58), allogeneic mesenchymal stromal cells (59), etc. needs to be explored.

CONCLUSION

The quality of currently available evidence for using RET for resorption cases ranges from low to moderate. All the cases except one included in this review reported the arrest of resorption after RET. Hence it could be considered an alternative treatment option for root resorption provided further reliable evidence is available.

Disclosures

Conflict of interest: The authors deny any conflict of interest.

Peer-review: Externally peer-reviewed.

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