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Determinants of Success in Regenerative Endodontic Procedures: A Narrative Review

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Abstract

Regenerative endodontic procedures (REPs) have emerged as a biologically driven alternative to apexification in immature necrotic teeth. This narrative review synthesizes current evidence on the key factors influencing REP outcomes, including case selection, disinfection protocols, scaffold induction, and coronal sealing. Literature published between 2017 and 2024 was reviewed from PubMed and Medline, focusing on clinical studies and systematic reviews. Success is associated with minimal instrumentation, effective intracanal disinfection, induction of apical bleeding, and biocompatible sealing. Patient age, apical diameter, and procedural standardization also play critical roles. REPs, when properly indicated and executed, support root maturation and periapical healing.

Keywords: Immature permanent teeth ,MTA ,revitalization

1. Introduction

Tissue regeneration has become one of the most significant areas of research in the 21st century, driven by advancements in biology, regenerative medicine, and tissue engineering (1). In dental medicine, regenerative techniques have particularly focused on dental pulp regeneration through regenerative endodontic procedures (REPs). These biologically-based approaches integrate tissue engineering principles to repair and replace damaged structures, such as dentin and pulp-dentin complex cells. The objective of REPs is not only to heal apical lesions and alleviate clinical symptoms but also to promote continued root development and strengthen dentinal tissues, which may prevent future root fractures (2).

The first documented case of revascularization was published in 2001 (3), and over the years, clinical experience has led to the establishment of success criteria for REPs. These criteria include the resolution of clinical signs and symptoms, continued root maturation (e.g., increased thickness of the root canal walls and/or root length), and re-establishment of neurogenesis or a positive response to vitality tests (4).

Numerous case studies have contributed to the evolving understanding of regenerative endodontics, revealing a range of outcomes, both successful and unsuccessful. These studies have shaped clinical practices and contributed to the consensus within the field, with various factors such as pulp pathology, patient age, technique employed, and material quality influencing the success rates of REPs.

The American Association of Endodontists (AAE) has developed a standard protocol for revascularization, which includes endodontic disinfection, induction of bleeding, and coronal restoration (5).

Materials and Methods

Eligibility Criteria

Inclusion Criteria:

Studies that discuss case selection, clinical protocols, intracanal medications, and coronal restoration in regenerative endodontic procedures (REPs).

Studies published in English between 2017 and 2024

Types of studies: systematic reviews, meta-analyses, cohort studies, and clinical trials.

Exclusion Criteria:

Studies involving non-human subjects.

Studies focused on mature permanent teeth or primary teeth.

Case reports or descriptive studies with fewer than five cases.

Studies published in languages other than English.

Information Sources

A comprehensive search was performed in PubMed and Medline databases for articles published between 2017 and 2024. The search terms used included "Immature permanent teeth," "MTA," "revitalization," and "regenerative endodontic procedure."

Study Selection Process

Two independent reviewers initially screened the titles and abstracts of the identified articles for relevance to the topic. Disagreements were resolved by discussion or by consulting a third reviewer. Full-text versions of the selected studies were then reviewed to determine their eligibility based on the inclusion and exclusion criteria.

Data Extraction and Management

Data extraction was conducted by two independent reviewers. The extracted data included case selection criteria, clinical protocols for disinfection, intracanal medications, coronal restoration techniques, and the reported outcomes. The data were organized into a standardized format for consistency and easier comparison.

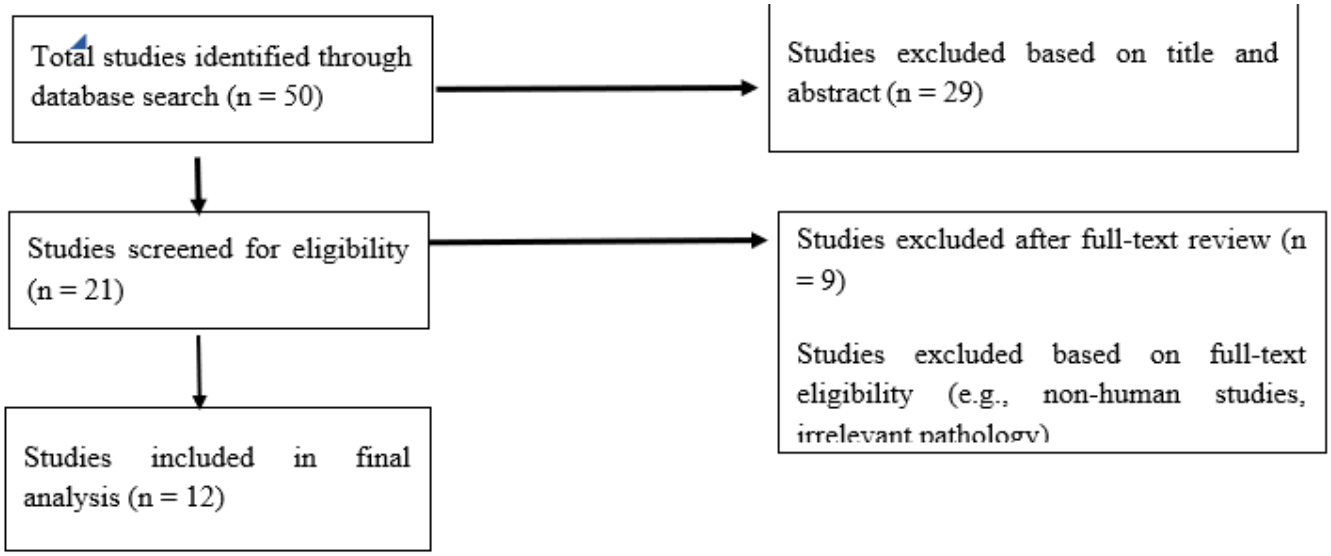
Risk of Bias Assessment

The quality of the included studies was assessed using appropriate tools based on the study design. For randomized controlled trials (RCTs), the Cochrane Risk of Bias Tool was used. For cohort studies, the Newcastle-Ottawa Scale was applied. The risk of bias was evaluated in several domains, including selection, performance, detection, and reporting biases.

Results

1. Identification of Studies

(PubMed and Medline, 2017-2024)



Study Selection

A total of 23 studies were identified from the initial search. After screening, 12 studies met the inclusion criteria and were included in the final analysis. These studies were classified into two groups:

1. **Case Selection**: 5 studies
2. **Clinical Protocols**: 7 studies

Case Selection Criteria

The five studies on case selection identified several key factors that influence the success of REPs:

- **Age**: Younger patients (under 18 years) generally showed better regenerative potential.
- **Pulp Pathology**: Most studies indicated that REPs were effective for treating necrotic pulp or irreversible pulpitis.
- **Apical Diameter**: An apical diameter greater than 1 mm was recommended for successful outcomes.
- **Systemic Health**: Studies emphasized that no significant systemic contraindications were found to exclude patients from REPs.

Case Selection

Table 1: Criteria for Case Selection in Regenerative Endodontic Procedures

Article	Year	Patient Age	Pulp Pathology	Apical Diameter
Hameed et al. (5)	2019	Young patient	Not mentioned	0.5 to 1 mm
Staffoli et al. (6)	2019	6–18 years	Minimal duration of infection	> 1 mm
Murray et al. (7)	2022	6–17 years	Necrotic pulp or irreversible pulpitis	> 1.1 mm
Krastl et al. (8)	2021	Young patient	Non-vital pulp	Open apex
Zeng et al. (9)	2022	9–14 years	Dens evaginatus, better outcomes than dental trauma	> 1 mm

Clinical Protocol:

The 7 studies on clinical protocols provided detailed information on the methods used for disinfection, intracanal medication, and sealing materials:

- **Irrigation**: Sodium hypochlorite (NaOCl) was the most commonly used irrigant, with concentrations ranging from 1.25% to 6%.
- **Intracanal Medications**: Calcium hydroxide (Ca(OH)2) and triple antibiotic paste (TAP) were the most widely used intracanal medications.
- **Sealing Materials**: Mineral trioxide aggregate (MTA) was the preferred material for sealing the canal orifice, although alternatives such as Biodentine and Endosequence bioceramic materials were also explored.

Table 2: **Clinical Protocols Used in Regenerative Endodontic Procedures**

Article	Year	Disinfection	Intracanal Medication	Induction of Bleeding	Sealing of Canal Orifice
Hameed et al. (5)	2019	1.5% NaOCl + saline	Triple antibiotic paste (TAP)	Over-instrumentation + CollaPlug	MTA
Staffoli et al. (6)	2019	6% NaOCl, 17% EDTA, then 6% NaOCl	Ca(OH)2 (3-4 weeks)	File with small bend in EDTA	Endosequence Bioceramic Putty, Biodentine, MTA
S. Adam et al. (10)	2020	2.5–6% NaOCl and 17% EDTA	Ca(OH)2 or 0.1 mg/ml TAP	Not mentioned	MTA
Mishra et al. (11)	2022	1.25% NaOCl, EDTA	Ca(OH)2 or 0.1 mg/ml TAP	PRF	MTA
Saxena et al. (13)	2022	Not mentioned	Ca(OH)2	PRF	MTA or Biodentine

Discussion

Factors Affecting REP Outcomes: Several factors influence the success of regenerative endodontic procedures, including case selection, irrigation protocol, intracanal medications, and the final sealing of the canal.

1. **Case Selection**:
   - The most favorable outcomes are seen in young patients (6-18 years), who exhibit a higher regenerative potential due to their more active stem cell populations (5).
   - Pulp pathology plays a significant role, with irreversible pulpitis and necrosis being the most common indications. However, the duration of the infection is a key factor, with minimal infection duration yielding better outcomes (6) (7).
   - Apical diameter is crucial, with an ideal size of at least 1 mm to ensure adequate bleeding and clot formation for pulp regeneration (6) (7).
   - Dens evaginatus has shown a better prognosis compared to traumatized teeth (9).
2. **Irrigation Protocol**:
   - Sodium hypochlorite (NaOCl) is the most widely used irrigant due to its effective antibacterial properties. However, higher concentrations (6%) can be cytotoxic to stem cells. The commonly used

concentration is 1.25%, which balances antibacterial efficacy and stem cell preservation (10).

- The use of 17% EDTA following NaOCl has been shown to partially mitigate NaOCl's harmful effects on stem cells (10). Other alternatives like propolis and ascorbic acid have shown promise in reducing cytotoxicity while maintaining adequate disinfection (14).

3. **Intracanal Medications**:

- **Calcium Hydroxide (Ca(OH)2)**: It has a strong antibacterial effect due to its high pH. However, prolonged contact with stem cells can be cytotoxic, so it should be applied coronally to avoid direct contact with the root canal cells.
- **Triple Antibiotic Paste (TAP)**: This paste, composed of ciprofloxacin, metronidazole, and minocycline, has broad-spectrum antibacterial properties but can cause discoloration due to minocycline. TAP should be applied at concentrations of at least 5 mg/ml to avoid cytotoxic effects on stem cells (5).
- **Double Antibiotic Paste (DAB)**: An alternative to TAP, DAB has shown promise due to its lower risk of discoloration, though further research is needed to confirm its long-term efficacy and safety (5).

4. **The induction of bleeding**

- The induction of bleeding is a critical phase in regenerative endodontic procedures, providing a natural scaffold rich in growth factors and stem cells essential for tissue regeneration. Mechanical over-instrumentation remains the most commonly used method, often facilitated by the use of EDTA to expose dentinal tubules and promote stem cell migration [5,6]. Collagen-based matrices such as CollaPlug may be used to stabilize the clot [5]. Alternatively, biologically active scaffolds like platelet-rich fibrin (PRF) have been introduced as substitutes, offering a controlled release of bioactive molecules and eliminating the need for apical manipulation [11,13]. While PRF shows promising regenerative potential, mechanical induction remains more accessible and reproducible in routine clinical settings. The choice between these methods should be based on clinical feasibility, anatomical considerations, and material availability.

5 **Sealing of Canal Orifice**:

- MTA remains the most commonly used material for sealing the canal orifice, due to its biocompatibility and sealing properties. However, alternatives like Biodentine and Endosequence Bioceramic Putty are also frequently used with good success in some cases.

Limitations of Current Protocols

While the existing literature provides valuable insights, there are several limitations that need to be addressed:

- The small sample sizes of many studies and the lack of long-term follow-up data limit the generalizability of findings.
- The variability in disinfection protocols, intracanal medications, and sealing materials makes it difficult to establish a universally accepted protocol.
- Most studies do not control for patient factors (e.g., systemic health, age), which may influence treatment outcomes.
- The technique for inducing bleeding remains a challenge, with inconsistencies in achieving controlled bleeding and clot formation.

Recommendations for Future Research

Future studies should focus on:

- Large-scale, multicenter clinical trials to validate and standardize protocols for REP.
- Long-term follow-up studies to assess the durability and effectiveness of regenerated pulp tissue.
- Exploration of newer biological alternatives (e.g., stem cell therapies, growth factors) to further enhance the regenerative potential of REP.
- Investigating the effects of patient-specific factors (e.g., age, systemic health) on treatment outcomes.

Conclusions

Regenerative endodontic procedures offer significant potential for the treatment of immature permanent teeth with pulp pathology. While traditional materials like calcium hydroxide and triple antibiotic paste continue to be widely used, emerging alternatives such as double antibiotic paste and ascorbic acid show promise for improving clinical outcomes. However, further clinical trials with larger sample sizes, longer follow-up periods, and more rigorous protocols are essential to establish these materials as viable treatment options. As the field evolves, personalized treatment approaches and the development of novel biomaterials will be crucial in optimizing outcomes and advancing the practice of regenerative endodontics

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