

Apexification and regeneration procedures in young permanent teeth

Utku Yasemin Yılmaz¹ , Mesude Eskici^{1,2} , Ceyda Kerimoğlu¹ , Tuğba Bezgin¹ 

¹ Ankara University, Faculty of Dentistry, Department of Pedodontics, Ankara, Türkiye

² Ankara University, Institute of School of Health Sciences, Department of Pedodontics, Ankara, Türkiye

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Correspondence:

Dr. Tuğba BEZGİN

Ankara University, Faculty of Dentistry,
Department of Pedodontics, Ankara,
Türkiye.

E-mail: cetintugba@yahoo.com



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Abstract

Management of necrotic young permanent teeth with incomplete root development represents a significant clinical challenge in pediatric dentistry due to open apices, thin dentinal walls, and increased susceptibility to fracture. Preserving or restoring root development is critical for improving the long-term prognosis of these teeth. Over recent decades, apexification and regenerative endodontic procedures (REPs) have emerged as the primary treatment strategies for addressing pulp necrosis in immature permanent teeth. Apexification aims to induce the formation of a calcified apical barrier that allows effective obturation of the root canal system. Traditionally, calcium hydroxide has been widely used for this purpose, demonstrating high success rates in resolving apical pathology. However, prolonged treatment duration, increased risk of root fracture, and lack of continued root development are important limitations. To overcome these drawbacks, single-visit apexification using bioceramic materials such as mineral trioxide aggregate (MTA) has gained popularity, offering predictable apical barrier formation, reduced treatment time, and favorable clinical outcomes. Regenerative endodontic procedures represent a biologically based treatment approach designed to promote continued root maturation by harnessing the regenerative potential of stem cells from the apical papilla, growth factors, and suitable scaffolds. REPs aim not only to resolve infection but also to facilitate root lengthening, thickening of dentinal walls, apical closure, and reestablishment of vitality-related responses. Clinical studies have reported high survival and success rates for REPs, particularly in teeth with short roots and wide apical openings. This review provides a comprehensive comparison of apexification and regenerative endodontic procedures, focusing on their biological principles, clinical protocols, indications, advantages, and limitations. Emphasis is placed on evidence-based decision-making to guide clinicians in selecting the most appropriate treatment modality based on individual case characteristics. Understanding the strengths and shortcomings of each approach is essential for optimizing clinical outcomes and preserving young permanent teeth in pediatric patients.

Keywords: Apexification, calcium hydroxide, pulp regeneration, single-visit apexification

1. Introduction

A young permanent tooth is defined as a newly erupted permanent tooth with an incomplete root formation. The pulp tissue in these teeth has the potential for regeneration due to the wide-open apex/apices, rich blood circulation, and the presence of abundant stem cells in the apical region (1). Since root development is completed 2-3 years after the tooth erupts into the oral cavity, the loss of pulp vitality in young permanent teeth should be prevented as much as possible, and the continuation of apexogenesis should be ensured (2, 3).

Root formation and maturation require complex interactions between mesenchymal cells located in the apical papilla and the epithelial root sheath (4). Dentin caries or trauma can disrupt this interaction, leading to necrosis and interruption of tooth development (5). Treating necrotic immature teeth presents a challenge for clinicians because of the open apex and weak root structures, making the application of conventional endodontic treatments difficult. Traditionally, treatment options for these teeth include long-term calcium hydroxide ($\text{Ca}(\text{OH})_2$) application for apexification, single-visit apexification (creating an apical barrier with a bioceramic material), and regenerative endodontic procedures (REPs) (2, 6, 7).

Apexification is a method that promotes the development of an apical barrier, allowing the placement of filling materials into the root canal space (8). Regenerative endodontic procedures (REPs) are biologically based procedures designed to replace damaged structures, such as the root and dentin, with cells from the pulp-dentin complex (9). The primary aim of REP is to create a suitable environment (biomimetic microenvironment) in the root canal to facilitate pulp tissue regeneration and root development by utilizing mesenchymal stem cells, such as osteogenic/odontogenic progenitors. The fundamental principle underlying both treatment methods is infection control (10). REP is recommended for teeth with short roots, thin canal walls, and a wide-open apex, whereas apexification techniques are recommended for teeth where root formation is nearly complete (11).

The purpose of this review was to comparatively evaluate these treatment methods used for necrotic young permanent teeth.

2. Apexification

Apexification is defined as "a method for creating a calcified barrier in a root with an open apex or the continued apical development of an immature root in teeth with necrotic pulp" (12). The calcified barrier formed can consist of dentin, cementum, bone, and osteodentin (13). Since the 1960s, apexification has been the preferred treatment method for immature permanent teeth with pulp necrosis (2, 12, 14). In a

retrospective study of 98 teeth treated with apexification, more than 90% success was achieved in resolving apical periodontitis over a long-term follow-up period (15). Other studies have also reported nearly 100% success in resolving apical periodontitis in teeth with open apices (16, 17).

However, one of the main limitations of apexification is that when it is applied to immature teeth with a wide-open apex and thin, short root structure, three-dimensional root development does not continue post-treatment. Consequently, the risk of root fracture increases in teeth treated with apexification. It has been reported that the incidence of cervical root fracture after treatment is significantly higher in teeth with incomplete root development compared to mature teeth (5). Additionally, the failure of the root to lengthen leads to an unfavorable crown-to-root ratio, negatively affecting the prognosis of the tooth (2).

Calcium hydroxide (CH) is widely used material in dentistry because of its biological compatibility with the pulp and periodontal tissues. It was first used in apexification treatment by Frank and is referred to in the literature as the "Frank technique" (14). The success rate of apexification treatment using calcium hydroxide ranges from 74% to 100% in previous studies (18, 19).

The success of calcium hydroxide in apexification is achieved through several mechanisms: ensuring asepsis in periapical tissues, transforming undifferentiated mesenchymal cells into cementoblasts, accelerating cementogenesis at the apex, promoting calcification under the necrotic layer formed due to its high pH, filling the canal space to prevent granulation tissue from advancing into the canal, activating alkaline phosphatase and pyrophosphatase enzymes while inhibiting osteoclastic activity, and ultimately forming a hard tissue barrier through the combined action of these mechanisms (8, 18).

The first stage of treatment is to disinfect the root canal system to promote periapical healing. After the tooth is isolated with a rubber dam, a wide endodontic access cavity is opened to reach the necrotic tissues. Once all necrotic pulp tissue is removed using a K-file, gentle circumferential filing is performed up to 1 mm short of the radiographic apex, followed by copious irrigation with 2.5% sodium hypochlorite (NaOCl) to disinfect the tooth. Final irrigation is performed with a sterile saline solution, and the canal is dried using sterile paper points set to the appropriate working length. Next, calcium hydroxide, mixed to a creamy consistency, is placed into the canal, carefully maintaining the working length. A dental syringe marked for the working length should be used for placing the paste rather than a lentulo spiral. After placing a cotton pellet in the cavity, a temporary filling is applied to the tooth (20, 21). Calcium hydroxide should remain in the canal for approximately one week to exert its disinfecting effect (22). After 7-10 days, the paste is refreshed. If there are no symptoms, subsequent appointments are scheduled at 2-3-month intervals, with the paste being renewed at each visit. The intervals should not exceed the specified time, as calcium hydroxide can be diluted by tissue fluids via the

open apex, making the canal susceptible to reinfection and delaying hard tissue barrier formation (20, 21). After 4-5 follow-up sessions, the hard tissue barrier will be radiographically visible, indicating that the canal is ready for obturation (18, 21).

However, even with current technology, it is not entirely possible to completely remove CH from the canal before final obturation with gutta-percha and root canal sealer. Residual CH reduces the adaptation of root canal sealers to the canal walls during final obturation (23, 24). Long-term CH application alters the protein structure of dentin, increasing its brittleness (5, 25, 26). Another significant disadvantage of this treatment method is that it can be extended up to two years. The drawbacks of this prolonged period include the need for multiple patient visits and the potential for coronal leakage due to the loss of temporary filling material, leading to reinfection between sessions (6, 27, 28). As a result, apexification has become a method preferred today primarily for teeth with completed root length and minimal apical opening (2).

2.1 Formation of a Hard Tissue Apical Barrier with Bioceramic Material (Single-Visit Apexification)

An alternative treatment to long-term calcium hydroxide (CH) apexification is the "single-visit apexification" method, which involves creating an apical barrier in a single session. This method is defined as "the non-surgical compaction of a biocompatible material into the apical portion of the root canal" (29, 30). This approach allows for the completion of permanent root canal filling in a shorter time and supports periapical healing (30-32).

Studies recommend covering the apical 3 to 5 mm of the root with a biological material to create an ideal, leak-proof barrier (33-36). An ideal material should be radiopaque, biocompatible, bacteriostatic, insoluble in tissue fluids, dimensionally stable, easy to prepare and use, have an appropriate setting time, possess biomimetic properties, and be nontoxic (37, 38).

In the past, materials such as tricalcium phosphate, freeze-dried dentin, or cortical bone were used to quickly form a hard tissue barrier after canal disinfection. Today, calcium silicate-based agents, such as mineral trioxide aggregate (MTA), Biodentine, and Bioaggregate, etc., are successfully used for this purpose. Numerous articles on the use of bioceramics for the apical barrier technique have been published, and this method has gained increasing popularity among clinicians (39-43).

Mineral trioxide aggregate (MTA) is a calcium silicate-based cement widely used in endodontic procedures such as pulp capping, pulpotomy, apexification, perforation repair, root-end filling, and pulp regeneration (44). MTA was developed by Torabinejad et al. in 1993 and was first introduced in dentistry in the 1990s. MTA has been reported to induce

hard tissue formation more effectively than calcium hydroxide, and it has shown very high clinical and radiographic success rates as a root-end filling material in immature permanent teeth (22, 45). Various in vitro and in vivo studies have demonstrated that MTA prevents microleakage, is biocompatible, and supports the regeneration of original tissues when placed in contact with dental pulp or periradicular tissues (46-48).

In the clinical procedure for single-visit apexification, after the initial steps are followed as previously described, the canals are dried using sterile paper points. Then, MTA or a similar bioceramic material is then placed in the apical 4-5 mm section of the canal. The placement, density, and thickness of the apical bioceramic plug should be evaluated using radiographic images. The coronal root canal space can be filled with MTA, similar bioceramic material, or warm gutta-percha. Finally, the permanent restoration of the tooth is completed (1).

Alternatively, to prevent the extrusion of MTA or other bioceramic materials into the periapical tissues, a 3 mm thick biocompatible absorbable collagen matrix is placed in the apical canal approximately 1-2 mm short of the canal length. Absorbable collagen membranes can be mechanically shaped, adapted, and easily manipulated for clinical applications (49).

Then, a 3 mm thick bio-ceramic plug is placed on top of the collagen matrix. The remaining coronal canal space is filled with warm gutta-percha. The access cavity is restored with permanent restorative materials. The collagen matrix in the apical canal is absorbed over time, leaving a 3-4 mm apical canal space unfilled to allow for continued apical root development. Researchers have argued that this technique ensures the continuation of apical root development by preserving Hertwig's epithelial root sheath cells (thickening of the apical canal walls, increased root length, and apical closure) (50, 51).

3. Regenerative Endodontic Procedure

Regenerative endodontic procedures are contemporary treatment methods applied to immature necrotic teeth. This treatment approach is based on a biological concept that relies on three key elements: stem cells, tissue scaffolds, and growth factors, aimed at rejuvenating the pulp-dentin complex, thereby promoting root lengthening, apical closure, dentin formation, and healing of periapical lesions (52-55).

REPs continue to achieve high survival and success rates in immature permanent teeth with necrotic pulp and/or apical periodontitis (32, 56-58), contributing to the regression of clinical signs and symptoms, healing of apical lesions, increase in root wall thickness/root length, and continuation of root maturation, as well as the response to pulp sensitivity tests, indicating the restoration of neurogenesis. Unlike traditional endodontic treatment, after REP, disinfected root canals

are filled with newly regenerated vital tissues, providing an immunoinflammatory defense mechanism to combat bacteria and control reinfection of the root canal system (59).

The concept of pulp tissue regeneration was first introduced in the 1960s by Nygaard-Østby, who formed the foundation of regenerative endodontics (60). In 2001, Iwaya et al. successfully induced root development and restored pulp sensitivity in a young permanent tooth with apical periodontitis using a revascularization method (61). In 2004, Banchs and Trope reported a case that provided evidence for the clinical application of regenerative endodontics using a modified revascularization protocol. They created a blood clot as a matrix for new tissue growth following the disinfection of the canals and performed a hermetic coronal restoration to prevent bacterial invasion into the pulp space (62). Since the first reported case in 2001, there has been an increase in studies using regenerative endodontic treatments (RETs) to treat young permanent teeth with apical periodontitis (7, 56, 63-66).

To date, a search of PubMed using the keywords "revascularization," "revitalization," and "regenerative endodontics" yields over 600 articles. These articles include basic research, case reports, case series, retrospective studies, prospective clinical studies, reviews, and guidelines. Currently, two guidelines for RETs are available for dentists. The American Association of Endodontists (AAE) published its clinical guideline in 2013, updating versions in 2016, 2018, 2021, and 2022 (67). The European Society of Endodontology (ESE) also released a statement in 2016, presenting similar procedural details but with some differences regarding the choice of medicaments, blood clot formation, placement of base materials, and success criteria for RETs (68).

For a successful regenerative endodontic treatment (RET), the formation of a blood clot within the tooth is necessary. After regenerative endodontic treatment, 25% of treatment failures have been attributed to a lack of bleeding (69), which can be interpreted as the inability to achieve sufficient revascularization of the root canal. Blood flow from the periapical tissues into the root canal and filling of the root canal space are essential for revascularization (69,70). Without adequate blood flow, revascularization cannot occur, and new pulp-like tissue cannot be formed to mineralize the dentin walls and continue root development.

It is noted that fragile, immature permanent teeth in young patients aged 6-9 with thin dentin walls are the ones that would benefit most from RET (69). This is because this treatment method thickens the dentin walls, allowing root development to continue and strengthening the teeth to withstand fractures under excessive stress (71). Studies on replantation and autotransplantation, it has been shown that pulpal revascularization occurs more easily in immature permanent teeth with shorter roots (<8 mm) and larger apical foramina (>1 mm) (72, 73).

3.1 Regeneration—Clinical Protocol

According to the AAE clinical protocol for regenerative treatment, the indication criteria are as follows: teeth with necrotic pulp and immature apex that can be permanently restored, patients who are compliant along with their parents, and those who do not have allergies to medications or antibiotics used in the procedure (ASA 1 or 2). However, patients with any systemic disease that could compromise blood clotting, such as hemophilia or von Willebrand disease, or those taking blood-thinning medications (anticoagulants), are at significant risk for uncontrolled bleeding (74). Therefore, it is not recommended to provoke bleeding in these patients because of the risk of tissue damage.

In the informed consent form obtained from patients, it should be noted that this procedure may require two (or more) appointments, antimicrobial agents will be used, and there are potential adverse effects, such as tooth discoloration, failure to respond to treatment, and pain/infection. Patients should also be informed about alternative treatment options, such as apexification, not proceeding with treatment, or tooth extraction (67).

At the first appointment, after applying local anesthesia to the tooth, a rubber dam is placed, and the access cavity is opened. Using an irrigation system that minimizes the likelihood of irrigant extrusion into the periapical space (e.g., a closed-ended and side-vented needle), gentle irrigation is performed in each canal with 20 ml of 1.5% NaOCl for 5 min. Subsequently, each canal is irrigated with sterile saline for 5 min, followed by a final irrigation with EDTA (20 ml per canal for 5 min). The irrigation needle should be positioned approximately 1 mm away from the root tip to minimize cytotoxicity to the apical stem cells. After gently drying the canals with paper points, calcium hydroxide or a low-concentration triple-antibiotic paste is placed. The triple antibiotic paste is prepared by mixing ciprofloxacin, metronidazole, and minocycline in a 1:1:1 ratio at 1-5 mg/ml concentration. Minocycline in the triple-antibiotic paste has been associated with tooth discoloration; therefore, a minocycline-free double-antibiotic paste (ciprofloxacin and metronidazole) or other third antibiotics (e.g., clindamycin, amoxicillin, and cefaclor) are recommended. After sealing the tooth with a temporary restorative material, the patient is scheduled for a follow-up appointment in 1-4 weeks.

In the second appointment, the response to the initial treatment is evaluated. If there are ongoing signs or symptoms of infection, additional treatment with alternative antimicrobials should be considered. After providing anesthesia with 3% mepivacaine without a vasoconstrictor, the tooth is isolated with a rubber dam, and gentle irrigation is performed in each canal with 20 ml of sterile saline for 5 min, followed by 20 ml of 17% EDTA for 5 min per canal, and then 5 ml of sterile saline per canal. After drying the canals with paper points, over-instrumentation of the tooth is performed to induce bleeding by inserting a pre-curved K-file 2 mm beyond

the apical foramen, ensuring that the canal orifices fill with blood up to the cemento-enamel junction. A slightly moist sterile cotton pellet is placed in the cavity, and clotting is allowed for 15 min. Alternative methods for creating a blood clot include the use of platelet-rich plasma (PRP), platelet-rich fibrin (PRF), and autologous fibrin matrix (AFM) (56). A calcium silicate-based material is placed over the blood clot, followed by a layer of glass ionomer cement, and then the permanent restoration is completed.

The success of regenerative endodontic procedures is largely measured by the extent to which primary, secondary, and tertiary goals are achieved. The current AAE guidelines define the success of REPs based on the following three criteria:

- **Primary goal:** Elimination of symptoms and evidence of bone healing.
- **Secondary goal:** Increased root wall thickness and/or root length.
- **Tertiary goal:** Positive response to pulp sensitivity testing.

Although RET has clearly revolutionized the treatment of immature teeth with pulp necrosis, the current procedure falls short of fully regenerating the dentin-pulp complex. Histological studies conducted on these teeth have revealed the absence of organized pulp tissues and the occurrence of ectopic tissue formation within the root canal lumen, including bone, cementum, and fibrous tissues (55, 75). This formation may manifest as extensive calcifications visible on follow-up radiographs.

The most common complications of REPs are pain, tooth discoloration, and intracanal calcification (76). Pain may occur between sessions or after treatment is fully completed. Pain during treatment can result from mechanical irritation of the periapical tissue due to incorrect working length calculation during root canal preparation and irrigation. To prevent this, the working length should be confirmed at the start of treatment and carefully maintained throughout the procedure.

In the literature, tooth discoloration has been reported as a frequent complication of REPs, significantly impacting patient satisfaction and quality of life (77). Patients, especially for anterior teeth, expect both aesthetic outcomes and successful treatment results. Discoloration can be attributed to various factors, such as disinfecting agents, bleeding, and barrier materials. Intracanal medicaments are used to disinfect root canals during endodontic treatments. Triple antibiotic paste containing ciprofloxacin, metronidazole, and minocycline has been used as a disinfectant in REPs for over 20 years. However, as mentioned earlier, a key issue with this paste is its inclusion of minocycline, which can cause significant tooth discoloration owing to its ability to chelate calcium ions, integrate into dentin tissue, and synthesize oxidation products (78).

Researchers have noted that in 62% of RET cases, varying degrees of intracanal calcification were observed, with some cases showing complete canal

obliteration. This is a common treatment complication and can pose an obstacle for performing root canal treatment in unresolved cases (79).

Berkhoff et al. reported that the antibiotic paste can be found up to 350 µm deep within the dentin walls, and no matter how extensively irrigation is performed, approximately 88% of the paste remains in the root canals (80). Therefore, the AAE recommends using the paste at a low concentration, covering the pulp chamber immediately with a dentin bonding agent to minimize the risk of staining, and keeping the paste below the cemento-enamel junction (67). Alternatively, other antibiotics such as clindamycin, amoxicillin, and cefaclor can be used in place of minocycline to prevent staining (76).

4. Conclusion

Currently, both REP and apexification procedures are widely and successfully applied to necrotic young permanent teeth, as evidenced by positive outcomes in the literature. Each method has its own advantages and disadvantages. The clinician must choose which method to use based on the properties of the case and the patient/parent. In addition, clinicians must appropriately implement both methods in accordance with the procedural guidelines.

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