Regenerative Endodontics for Adult Patients

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Abstract

The goal of endodontics is to save teeth. Since inception, endodontic treatments are performed to obturate disinfected root canals with inert materials such as gutta-percha. Although teeth can be saved after successful endodontic treatments, they are devitalized and therefore susceptible to reinfections and fractures. The American Association of Endodontists (AAE) has made a tremendous effort to revitalize disinfected immature permanent teeth in children and adolescents with diagnoses including pulp necrosis or apical periodontitis. The American Dental Association (ADA) in 2011 issued several clinical codes for regenerative endodontic procedures or apical revascularization in necrotic immature permanent teeth in children and adolescents. These AAE and ADA initiatives have stimulated robust interest in devising a multitude of tissue engineering approaches for dental pulp and dentin regeneration. Can the concept of regenerative endodontics be extended to revitalize mature permanent teeth with diagnoses including irreversible pulpitis and/or pulp necrosis in adults? The present article was written not only to summarize emerging findings to revitalize mature permanent teeth in adult patients but also to identify challenges and strategies that focus on realizing the goal of regenerative endodontics in adults. We further present clinical cases and describe the biological basis of potential regenerative endodontic procedures in adults. This article explores the frequently asked question if regenerative endodontic therapies should be developed for dental pulp and/or dentin regeneration in adults, who consist of the great majority of endodontic patients. *(J Endod 2017;43:S57–S64)*

Key Words

Cell homing, dental pulp, dentin, endodontics, regeneration, regenerative, tissue engineering

Significance

Although teeth are saved after successful endodontic therapy, they are devitalized and therefore susceptible to reinfections and fractures. The AAE and ADA have advocated revitalization of necrotic immature permanent teeth in children and adolescents. This article not only summarizes emerging findings to revitalize mature permanent teeth in adults, but also identifies challenges to regenerate dental pulp and/or dentin in adult patients. Novel strategies including protein delivery, cell delivery, and biomaterials application are discussed.

Since the dawn of endodontic treatment, inert materials have been used to seal disinfected root canals. The operating philosophy of contemporary endodontics is to disinfect and obturate by filling the instrumented root canals with inert materials and minimizing the space for microbial reinfections. There is no question that current endodontic treatments are successful in saving natural teeth (1, 2).

Like many successful medical/dental therapies, contemporary endodontic treatments are not without complications. Endodontically treated teeth are susceptible to reinfections and fractures. A recent large-scale study involving 64 network practices with a total of 1312 nonsurgical root canal patients in the United States showed an overall 19.1% failure rate in 3.9 $\pm$ 0.6 years after root canal therapy (3) (Table 1). Failure rates based on postoperative periapical radiolucency alone are approximately 23.3% and 25.3% for primary and secondary endodontic therapies in the United Kingdom, respectively (1, 2, 6) (Table 1). In Germany, the cumulative overall failure rate was 15.7% by 3-year recall among 556,067 root canal–treated teeth (4) (Table 1). An overall failure rate of 19.5% was found, with 17.2% $\pm$ 1.19% for root canal therapy in vital cases and 21.1% $\pm$ 1.05% for nonvital cases based on a meta-analysis published from 1966 through 2000 including a substantial number of Japanese cases (5) (Table 1).

Table 1 provides endodontic success and failure rates summarized from the previously referenced, large-scale studies, some including meta-analysis based on data from multiple regions of the world. Notably, the previously described failure rates represent endodontic treatments performed by general practitioners rather than endodontists. However, endodontic success and failure rates based on treatments delivered by general practitioners are of particular importance because approximately three quarters of endodontic treatments are performed by general dentists in the United States (and the remaining approximately one quarter by endodontists) (7), whereas the percentage of endodontic treatments delivered by general dentists elsewhere in the world is anticipated to be even higher. Success or failure after endodontic treatments is not binary but rather includes multiple conditions that define the health or disease status of

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TABLE 1. Endodontic Treatment Success and Failure Rates

Authors, year PMID	Country	Teeth/root canals	Failure rates (%)			Recall (years)
			Overall	Vital cases	Nonvital cases	
Bernstein et al, 2012 (3) PMID: 22547719	US	1312	19.1	—	—	3–5
Ng et al, 2007 (1) PMID: 17931389	UK*	15,544	25.3	17.5	26.9	0.5–20
Raedel et al, 2015 (4) PMID: 25676179	Germany	556,067	15.7	14.4	17.4	3[†]
Kojima et al, 2004 (5) PMID: 14716263	Japan*	9733	19.5[‡]	17.2	21.1	0.3–17

*Meta-analysis from multiple regions.

[†]Based on insurance data.

[‡]Calculated by weighing the percentages of vital and nonvital cases.

an endodontically treated tooth such as pain on percussion, apical radiolucency, and masticatory functions. With approximately 15 million root canal treatments in the United States per year and much more worldwide, a double-digit or even a single-digit failure rate would mean countless hours of retreatments or tooth loss, representing significant socioeconomic burden for the patient and society (8).

One of the key conclusions of a meta-analysis of 63 studies from 1922 to 2002 is that endodontic treatment success rates had not improved over the past 4 to 5 decades (1). Accordingly, a conceptual shift, rather than incremental technical improvements based on the existing endodontic philosophy, is necessary to improve endodontic success rates and further promote the longevity of natural teeth. Despite technology improvements, current endodontic therapy is based on the concept that disinfected root canals should be sealed with as little residual space as possible to minimize bacterial recolonization (9, 10). This concept was developed and improved over multiple decades before regenerative endodontic therapy was conceived. Bacterial colonies are in the nanometer range, whereas digital operating microscopes can view structures in the micrometer range (11). Additionally, bacterial colonies in the apical delta and/or lateral root canals are difficult to disinfect (10, 12). It is generally accepted that some bacteria or bacterial colonies are left behind after root canal disinfection and instrumentation (13). If dental pulp is regenerated, natural killer cells, lymphocytes, and macrophages are restored by blood vessels (14) and represent an innate immune system. Is it conceivable that space elimination for nanometer-sized bacteria and/or bacterial colonies by gutta-percha may be an "impossible mission"? Innate immunity within the root canal, which is disallowed after conventional endodontic treatment and can be restored after regenerative endodontics, may offer the potential to reduce reinfections. Furthermore, regenerated tissues may be structurally more resistant to fracture than endodontically treated teeth (15) (Table 2).

The American Association of Endodontists (AAE) states the following:

> "Regenerative endodontics is one of the most exciting developments in dentistry today and endodontists are at the forefront of this cutting-edge research. Regenerative endodontics uses the concept of tissue engineering to restore the root canals to a healthy state, allowing for continued development of the root and surrounding tissue. Endodontists' knowledge in the fields of pulp biology, dental trauma and tissue engineering can be applied to deliver biologically based regenerative endodontic treatment of necrotic immature permanent teeth resulting in continued root development, increased thickness in the dentinal walls and apical closure. These developments in regeneration of a functional pulp-dentin complex have a promising impact on efforts to retain the natural dentition, the ultimate goal of endodontic treatment."

The AAE's regenerative endodontics initiative has stimulated the development of multiple approaches for the revitalization of dental pulp in immature permanent teeth with pulp infections (16, 17). However, the AAE has limited its regenerative endodontics initiative to the revitalization of dental pulp and continuous root development in immature permanent teeth (18). The vast majority of endodontic treatments are in adults with well-developed, mature permanent teeth. Each year, approximately 15.1 million root canal procedures are performed in the United States alone, primarily in adults (19). The term of regenerative endodontics should include dental pulp and dentin regeneration in mature permanent teeth in adults. Broadly, there are 2 distinctive strategies for dental pulp and/or dentin regeneration in infected or traumatized mature permanent teeth in adults:

(1) Cell transplantation of *ex vivo* cultivated stem/progenitor cells or

TABLE 2. Comparison of Current Root Canal Therapy with Dental Pulp Regeneration

Approach	Current root canal therapy	Dental pulp regeneration
Goal	Eliminate space for bacterial recolonization	Restored native defense with natural killer cells, B and T lymphocytes, and antibodies
Clinical issues and solutions	Over- or underextension of root canal filling Thermal irritation	An injectable gel ensures complete fill of root canal; gelation within seconds Reduce radiographic exposure
Outcome	Nonvital teeth Susceptible to reinfections and fractures	Vital teeth Restored homeostasis and natural defense that may promote tooth survival