ENDODONTICS

Regenerative endodontics

A way forward

Anibal Diogenes, DDS, MS, PhD; Nikita B. Ruparel, DDS, MS, PhD; Yoav Shiloah, DDS, MBA; Kenneth M. Hargreaves, DDS, PhD

ABSTRACT

Background and Overview. Immature teeth are susceptible to infections due to trauma, anatomic anomalies, and caries. Traditional endodontic therapies for immature teeth, such as apexification procedures, promote resolution of the disease and prevent future infections. However, these procedures fail to promote continued root development, leaving teeth susceptible to fractures. Regenerative endodontic procedures (REPs) have evolved in the past decade, being incorporated into endodontic practice and becoming a viable treatment alternative for immature teeth. The authors have summarized the status of regenerative endodontics on the basis of the available published studies and provide insight into the different levels of clinical outcomes expected from these procedures.

Conclusions. Substantial advances in regenerative endodontics are allowing a better understanding of a multitude of factors that govern stem cell–mediated regeneration and repair of the damaged pulp-dentin complex. REPs promote healing of apical periodontitis, continued radiographic root development, and, in certain cases, vitality responses. Despite the clinical success of these procedures, they appear to promote a guided endodontic repair process rather than a true regeneration of physiological-like tissue.

Practical Implications. Immature teeth with pulpal necrosis with otherwise poor prognosis can be treated with REPs. These procedures do not preclude the possibility of apexification procedures if attempts are unsuccessful. Therefore, REPs may be considered first treatment options for immature teeth with pulpal necrosis.

Key Words. Guided tissue regeneration; revascularization; endodontic therapy; stem cells; outcome assessment; regenerative endodontics.

JADA 2016:147(5):372-380

http://dx.doi.org/10.1016/j.adaj.2016.01.009

Immature teeth are at risk of developing pulpal necrosis due to trauma, caries, and anatomic variations such as dens evaginatus and dens invaginatus.[1-4] Dental trauma occurs with an incidence that varies from 2.6% to 35% in patients undergoing cranioskeletal development.[5-7] Up to one-half of these traumatized teeth may undergo pulpal necrosis, but only 8.5% will exhibit signs and symptoms of disease.[8] Dental anomalies also represent a common etiology leading to pulpal necrosis in immature permanent teeth.[4] Dens evaginatus and dens invaginatus are the most common anomalies associated with this clinical manifestation.[4] Full radicular maturation occurs up to 3 years after the eruption of a tooth in the oral cavity,[9] and the loss of pulp vitality during this period arrests further root development. These teeth traditionally have been treated with apexification procedures by using either long-term calcium hydroxide treatment[10,11] or immediate placement of a mineral trioxide aggregate (MTA) apical plug.[12] Although these treatments often result in the resolution of signs and symptoms of disease, they provide little to no benefit in restoring normal pulpal defenses and nociception and, more importantly, continued root development.[13] Thus, immature teeth remain with thin fragile dentinal walls, increasing susceptibility to fractures and lower survival rates.[14,15]

Tooth loss in patients still undergoing cranioskeletal development has devastating consequences that include altered maxillary and mandibular bone development;

interference with pronunciation, breathing, and mastication; and a severe detrimental psychosocial effect.[16,17] Because implants are contraindicated in growing young patients because of continued craniofacial development, tooth replacement is not possible until the age of maturity (usually older than 18 years). As an alternative technique, regenerative endodontic procedures (REPs) are intended to promote tooth survival and the function of previously thought hopeless teeth. In this review, we will focus on discussing the historical background and the present and future directions of these clinical procedures.

HISTORY

The emergence of regenerative endodontics was catalyzed in the early 2000s with the publication of 2 remarkable case reports.[18,19] However, this field has its roots in the seminal work by Dr. Ostby in the early 1960s that aimed to evaluate the role of the apical blood clot in the healing of apical periodontitis and pulp repair.[20,21] Regenerative endodontics also relied on contributions from important studies in dental trauma, which provided evidence that the dental pulp in immature teeth often remains vital despite substantial traumatic injuries such as intrusions and avulsions.[22-24] This remarkable regenerative potential is highlighted in cases of replantation of avulsed immature teeth with evidence of reestablishment of vitality responses and lack of signs and symptoms of disease.[23,25,26] In these cases, clinical success relies heavily on the reestablishment of a blood supply to the ischemic but uninfected dental pulp tissue, followed by reinnervation from sensory axons likely recruited from the apical region. This healing process of a previously necrotic dental pulp in traumatic injuries is crucial for reattaining normal pulpal function after trauma. The term *revascularization* has emerged from these observations in dental traumatology despite the different application and goals.[4] Pulpal *revitalization* is another commonly used term in the scientific literature. However, for the sake of this review, we simply will address these procedures collectively as REPs. Results from numerous published reports demonstrate that these procedures often lead to resolution of apical periodontitis and signs and symptoms of inflammation, radiographic evidence of continued root development and apical narrowing, and restoration of vitality responses.[4,27,28] These published cases establish that REPs address the unmet need of promoting normal physiological development and responses in immature teeth with pulpal necrosis.

In most REPs, clinicians rely on creating bleeding from the apical region that passively fills the canal space and forms a blood clot. However, it was not until 2011 that investigators in a clinical study demonstrated that the influx of apical blood into disinfected root canals was accompanied by a clinically significant transfer of mesenchymal stem cells into the root canal system.[29] This was an important demonstration in the field of regenerative endodontics because it established that these procedures were, in fact, stem cell–based procedures. The realization that autogenous stem cells can be delivered clinically into root canals without the need for ex vivo stem cell expansion propelled researchers and clinicians to consider principles of tissue engineering to improve treatment protocols and to develop the next generation of procedures.

TRANSLATIONAL STUDIES

The balance between adequate disinfection and stem cell survival, proliferation, and differentiation represents an important initial barrier to overcome. The resolution of infection and the disease process remains the primary goal of any endodontic procedure. However, it has become obvious that the philosophy of disinfecting the root canal by using methods typically advocated in traditional root canal therapy had to be modified to attain a biocompatible disinfection strategy. To maintain the physical integrity of the already thin dentinal walls of immature teeth, investigators have advocated chemical debridement as the primary means of disinfection. To this end, investigators in many translational studies have focused efforts on establishing the biological basis for clinical protocols that could achieve both disinfection and optimum regenerative potential.[4,27] For example, sodium hypochlorite remains the most used disinfectant in endodontics.[30] However, its use at full concentration of 6% denatures crucial growth factors in dentin[31] and results in residual detrimental effects greatly affecting stem cell attachment, survival, and differentiation potential.[32-35] These deleterious effects largely can be avoided with the use of a 1.5% concentration of sodium hypochlorite followed by 17% ethylenediaminetetraacetic acid.[35,36] Furthermore, results from elegant studies have demonstrated that ethylenediaminetetraacetic acid promotes the release of growth factors embedded in dentin, including vascular endothelial growth factor and transforming growth factor beta-1 among others that are known to participate actively in regenerative processes such as angiogenesis and stem cell proliferation, migration, and differentiation, respectively.[37-39]

Along these lines, it was obvious that the effects of intracanal medicaments be tested on the survival and maintenance of stem cells. A triple antibiotic formulation consisting of ciprofloxacin, metronidazole, and minocycline first was tested in vitro against bacteria isolated from carious lesions and from endodontic infections in primary teeth.[40] The investigators found that no bacteria could be recovered after treatment with 100

ABBREVIATION KEY. MTA: Mineral trioxide aggregate. **NSRCT:** Nonsurgical root canal therapy. **REP:** Regenerative endodontic procedure.