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The Decision for Regenerative Endodontic Therapy

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Abstract

Regenerative endodontics is described as biologically based procedures designed to replace damaged structures, including dentin and root structures, as well as cells of the pulp-dentin complex, and is considered as an optimal approach for treating the immature permanent tooth with a necrotic pulp. Since the establishment of the foundations of regenerative endodontic therapy in 1960's a plethora of relevant clinical cases and studies have been published. However, until now the case selection as well as the clinical protocol applied during regenerative endodontic therapy have not been totally determined and supported by clinical studies with high level of evidence. This review summarizes the current literature regarding the prognostic factors and clinical outcomes of regenerative endodontic therapy and the various applied clinical protocols in terms of administration of mechanical instrumentation, irrigation, intracanal medicaments, intracanal bleeding and intracanal coronal barrier. The aim of this review is to clarify and determine all the factors that willcontribute to the decision making for the application of regenerative endodontic therapy.

Keywords

Regenerative endodontic therapy, Clinical protocols, Treatment outcome

Introduction

Regenerative endodontic procedures can be defined as biologically based procedures designed to replace previously damaged pulp-dentin complex by new vital tissue, resulting in restoration of the functional properties of the involved tooth [1,2]. Regenerative endodontic therapy (RET) holds a distinct role in the treatment of permanent immature teeth with open apices that suffer pulpal necrosis as a result of trauma or other insults [1,3]. In such cases, traditional, widely applied treatment techniques, like long term calcium hydroxide [$Ca(OH)_2$] apexification [4,5] or mineral trioxide aggregate (MTA) apical barrier techniques [5,6], do not reliably achieve the desired clinical outcomes, i.e. the healing of apical periodontitis, promotion of continued root development and restoration of the functional competence of pulpal tissue [1,7].

More than 50 years ago, this new approach of endodontic treatment was presented by Nygaard-Ostby who introduced a revascularization method for re-establishing a pulp-dentin complex in permanent teeth with pulpal necrosis [8,9]. The first case of revascularization of a permanent immature tooth with necrotic pulp and apical periodontitis was published in 2001 [10], and since then several publications showcased the biological or regenerative approach for endodontic treatment [3,11,12].

It must be stated that tissue regeneration refers to the formation of new tissue, reproducing both the anatomy and function of the original tissue and differs from tissue repair which is defined as the development of a replacement tissue, such as scar tissue, without restoration or function [13,14]. To fulfill this objective, regenerative endodontic procedures are based on 3 core principles of tissue engineering, requiring an appropriate source of stem/progenitor cells, growth factors capable of promoting stem cell differentiation and appropriate scaffolds in order to regulate the cell differentiation.

Current clinical protocols presented in clinical studies referring to RET meet theabove principles of tissue engineering. Stem cells are delivered into the root canal space from the periapical tissues; growth factors are released from either the intracanal blood clot or the platelet-rich plasma (PRP) or from dentin surfaces after proper condition with EDTA and blood clot or the PRP from the patient may serve as scaffolds. Necessary condition for long-term success of this treatment modality is the appropriate disinfection of the root canal system as well as the indispensable prevention from reinfection [15,16].

RET is a treatment modality that mainly confronts necrotic permanent immature teeth with open apices and is gradually gaining popularity. However, there are no data available that define all the discrete features that a case should fulfill to be treated with RET. The purpose of the present review is to provide an answer to the question of how the decisions of applying RET should be made and how safe such a decision can be, based on the available literature.

An Overview of Current Literature

Since the first publication of RET [10] several case reports, case series and a few clinical studies were published where immature permanent teeth with pulpal necrosis were treated with RET reporting varying clinical outcomes. Case reports and case series are studies that have a low level of evidence and, hence, the evidence provided by them cannot be considered definite for the efficacy and predictability of a given treatment.

A recent systematic review of the literature was published assigning levels of evidence to all the existing publications related to RET from 1993 to 2013 and evaluating their clinical and radiographic outcomes [17]. According to Kontakiotis et al. [17], in respect to

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RET, low-level clinical studies – consisting mainly of case series and case reports– dominate the literature, making evident the need for the conduction of randomized clinical trials. Therefore, since the level of best available evidence was not high enough, conclusions could not be drawn regarding the definite outcome of RET. However, the majority of teeth presented in the included studies exhibited resolution of the periapical radiolucency, continuation of root development and eventually apical closure. Few treated teeth failed to present increase in root length and root wall thickness after revitalization procedures [18-25].

The clinical outcome of RET can be assumed that is related to some prognostic factors like the etiology of pulp necrosis, especially in trauma cases, and long lasting periapical infections. Growth of new vital tissue inside the root canal after the regenerative procedures is presumably essential for the thickening of the root walls after the treatment [24]. On the other hand, root lengthening and apex formation are possibly related to maintenance of the integrity of Hertwig epithelial root seath (HERS) and its interaction with the mesenchymal cells of the periapex [26]. In cases where HERS's vitality has been lost, like in many cases of traumatized teeth, root formation will probably not occur [20,21,24,27]. Long lasting periapical infections can negatively affect root formation through the same mechanism, since in those cases the vitality of HERS is threatened [20,21,24].

According to the findings of the two cohort studies [7,28] included to this systematic review [17], RET resulted in a greater percentage of increase in root length and root wall thickness compared to $Ca(OH)_2$ apexification and the MTA apical barrier technique.

The cause of pulp necrosis, the presence or not of periapical disease, the longstanding nature of periapical disease, the patient's age, the type of tooth and also the quality of the used treatment protocol (mechanical and chemical agents) might be significant preoperative and intraoperative prognostic factors for the continuation of root development after the regenerative procedures. However, no further conclusions could be drawn from the literature included. Major differences among these articles regarding several prognostic and clinical factors, as well as the lack of standardization of a clinical protocol prevented the use and the combination of their results to determine prognostic factors on the outcome of RET [17].

An Overview of Clinical Protocols

The first clinical article that applied RET to an immature permanent tooth with apical periodontitis and sinus tract introduced an initial clinical protocol of the regenerative techniques [10]. This consisted of no mechanical instrumentation, in order to maintain the vitality of the stem cells inhabiting the periapical tissues. Regarding the root canal disinfection, sodium hypochlorite (NaOCl), and hydrogen peroxide (H_2O_2) were chosen as irrigation solutions and a mixture of antibiotics was chosen as an intracanal medicament. The 30-month postoperative radiograph exhibited apical closure of the root and thickening of the root walls.

Since this publication, a plethora of clinical studies, case series and case reports related to RET has been published, including a variety of differences in applied treatment protocols. This diversity concerns all the components of the applied techniques and materials during the administration of RET, including the mechanical instrumentation of canal walls, the utilized irrigation solution, the utilized intracanal medicament, the intracanal blood clot creation and the intracanal coronal barriers.

Further information regarding each of the components of RET mentioned above are gathered below, in order to provide to the clinicians a comprehensive perception of all the applied protocols of RET.

Mechanical Instrumentation of Root Canal Walls

According to Kontakiotis et al. in 68% of the clinical articles related to RET, the canal walls were not instrumented [29]. The concept of slight to no mechanical instrumentation of the root canal walls is based, according to the clinical articles and the clinical considerations of American Association of Endodontistis (AAE), to the rationale that the control of root canal infection should be achieved only by the use of irrigation solutions and intracanal medicaments [16,30,31]. Furthermore, mechanical debridement should be avoided in order to protect the vitality of stem cells in apical tissues, promoting tissue regeneration [16,31]. However, it is common knowledge that the colonizing bacteria organized in biofilms are extremely resistant to irrigants and intracanal medicaments [32,33]. There have been reported clinical cases of RET that failed mainly because of the remaining biofilm in root canal walls that were not mechanically debrided [34].

In an animal stud, it has been reported that the size of the apical foramen doesn't seem to be the critical decisive factor for successful revascularization and ingrowth of new tissue after transplantation [35]. Recently, RET was applied in mature teeth with necrotic pulp and complete root formation [36,37]. In a report of 2 cases, the mechanical instrumentation performed can be considered adequate, since the apical foramen was enlarged up to 0.60mm [36].

The real impact of mechanical instrumentation with regard to the root canal disinfection, as well as the possible jeopardy of the vitality of periapical tissues- which is the main source of stem cells- is still a matter of controversy.

Irrigation Solution

Irrigation protocols are another component of RET with crucial role [16,31]. NaOCl is included in the majority of clinical studies either as the only irrigantor in combination with other irrigants, in a concentration range from 1%-6% [29]. The clinical considerations of AAEsuggest the use of lower concentrations of NaOCl in RET [30]. Concentrations higher than 3%, although having favorable antimicrobial action, are considered to be cytotoxic to periodontal ligament cells and stem cells of apical papilla (SCAPs) [38,39].

Chlorexidine (CHX) is also being used in many clinical cases, either by itself or in combination with NaOCl at the first appointment of regenerative endodontic therapy [29]. Between the two mentioned irrigants the canal is irrigated with saline [3,25,40-48].The combined protocol is being applied as an effort to enhance the disinfection of the root canal by exploiting the additional antimicrobial activity of CHX and its substantivity [49,50]. Nevertheless, 2% CHX solution has been reported to induce serious cytotoxic effects on stem cells [51]. Probably due to this cytotoxicity CHX is not being used as the final irrigant in RET, as only 4% of the clinical studies included it in the final irrigation protocol [29].

In contrast to CHX, EDTA isoften included in the final irrigation protocol and only in publications after 2012 [29]. EDTA is considered to release various entrapped growth factors from dentin, promoting the differentiation of dental pulp stem cells seeded on dentin surfaces into odontoblastic cells [52]. It has been reported that an irrigation protocol including EDTA 17% promotes the survival of SCAPs [51], and that, when used as a final irrigant, EDTA can partially reverse the cytotoxic effects of high concentration NaOCl solutions on SCAPs. It seems that EDTA creates favorable environmental conditions for the promotion of tissue regeneration and its use may have a positive impact in RET.

Intracanal Medicament

In the majority of clinical articles, an antibiotic combination paste is being used as intracanal medicament [29]. In 1996 a mixture of 3 antibiotics (ciprofloxacin, metronidazole and minocycline) was proposed for eliminating bacteria located deep into the dentinal tubules [53]. Since then, a variety of antibiotic combinations have been used for the control of root canal infection. The wide use of antibiotics in RET is based on the ability of the antibiotic paste to eliminate the bacteria colonizing the dentinal tubules. The clinical considerations of AAE recommend the use of either antibiotic paste

or $Ca(OH)_2$ paste. In vitro studies have shown that antibiotic pastes in concentrations equal or higher than 1mg/mL are detrimental for the survival of SCAPs, unlike $Ca(OH)_2$ which promoted the SCAPs' proliferation [54,55].

Our team has completed several pilot, unpublished investigations regarding the impact of the two most commonly used intracanal medicaments in RET, the triple antibiotic paste and calcium hydroxide $Ca(OH)_2$, in the survival of stem cells from human exfoliated deciduous teeth (SHEDs). Our initial, currently unpublished results show that adhesion and proliferation of SHEDs in root canal surfaces that have been treated with $Ca(OH)_2$ are quantitatively and qualitatively greater compared to the root canal surfaces that have been treated with the triple antibiotic paste. Particularly, the SHEDs of the $Ca(OH)_2$ group appeared to have more distinct nuclei with widened characteristics rendering them more capable of survival, further proliferation and possibly differentiation. This finding opposes the prevalent clinical belief that $Ca(OH)_2$ should be avoided in RET due to its possible toxic effect in stem cells. The observed positive effect of $Ca(OH)_2$ might be due to the high pH conditions that prevail after its placement in the root canal, as well as to the impact of the released Ca ions. Another speculative mechanism that can lead to cell development is the release of growth factors embedded in dentin through alkaline hydrolysis.

Intracanal Blood Clot and the Use of Other Physical Scaffolds

The creation of a blood clot or the use of Platelet-rich plasma (PRP)/platelet-rich fibrin (PRF) is a part of the applied clinical protocol in most of the clinical articles related to RET [29]. The high prevalence of this method denotes the disagreement of clinicians on leaving the root canal space empty under the intracanal coronal barrier when applying RET. It has been reported that the formation of a blood clot promotes the accumulation of stem cells inside the root canal, promoting the desired tissue regeneration [56]. Except from providing a scaffold for the migration of stem cells into the canal space, the stable blood clot also serves as a source of growth factors [21]. The induction of intracanal bleeding in animal studies has been shown to improve the outcome of RET not only radiographically, but with histologic evaluation too [57].

In an effort to obtain better treatment results, recent protocols of RET therapy are using PRP or PRF instead of an intracanal blood clot [44,46,58-61]. PRF and PRP contain and secrete a large amount of growth factors that participate in tissue regeneration, and their application could be an option in cases of insufficient bleeding from periapical tissues [1,15,62].

Intracanal Coronal Barrier

Kontakiotis et al. after analyzing the clinical protocols of RET reported that the material of choice for the formation of an intracanal coronal barrier at the final session of RET is MTA [29]. The advantageous characteristics of this material, consisting of enhanced biocompatibility and bioactivity, have rendered it quite popular in clinical practice [63]. The introduction and application of contemporary bioceramic-based materials, with comparable biocompatibility and bioactivity with MTA [64,65], in RET should be evaluated, as it could be promising.

Our pilot, currently unpublished studies that evaluated the survival and adhesion of dental pulp stem cells (DPSC) in MTA-dentin specimens revealed that the presence of MTA in contact with dentin promotes the survival and adhesion of DPSCs irrespective of the presence and the size of voids in the material's surface. Adhesion of cells was observed even in the interface between dentin and MTA and is possible a result of the interaction of the material with the root canal surface which leads to hydroxyapatite formation, a biological molecule that promotes cell adhesion [66].

In several cases, the prior placement of a collagen matrix underneath the coronal intracanal barrier is being applied at this final session of RET [29]. The application of the collagen matrix was chosen either as a means of preventing the apical displacement of MTA [19], or in cases where little or no bleeding could be achieved when irritating the apical tissue during RET [11].The impact of a collagen matrix on the outcome of RET is another aspect that needs to be further investigated.

Conclusion

Undoubtedly, there is a need for randomized controlled trials related to RET. The lack of high-levels of evidence hinders the development of a well standardized clinical protocol along with a thorough determination of the prognostic factors on the outcome of RET. However, the existing studies reveal a treatment modality with very encouraging clinical and radiographic outcomes. The level of evidence available may not be ideal but this should not withhold the clinicians from the decision to administer to their patientsRET.

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