Endodontic Regenerative Procedures in Necrotic Adult Teeth

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Regenerative endodontic procedures (from now on REPs) have been defined as ‘biologically based procedures that intend to physiologically replace damaged tooth structures, including dentine and root, as well as cells of the pulp–dentin complex’. REPs were first exclusively developed for the treatment of immature teeth, with the purpose of achieving a complete root development. Nevertheless, these procedures can also restore tooth vitality and pulp functions thanks to the pulp tissue regeneration. Thus, sensibility, immunity, healing, and restorative properties of dental pulp would also be recovered, in turn reducing the chances of reinfection. For that reason, the feasibility of this treatment in mature teeth should be further studied, as until now, conservative treatment for irreversible necrosis or pulpitis has been limited to conventional endodontic therapy.

regenerative endodontics necrotic adult tooth clinical protocol

1. Introduction

Until now, conservative treatment for irreversible pulpitis or necrosis in adult teeth has been limited to conventional endodontic therapy. The high success of this technique is undeniable [1][2], with success percentages raging, according to the systematic review made by Ny et al. in 2010, from 83 to 93%, with a follow-up of 2 to 10 years [3]. Nevertheless, although the treatment would be successful, the tooth does not remain vital and, therefore, it is more susceptible to fracture and reinfection [4]. Performing REPs, it may be possible to restore these properties.

However, some conditions must be considered regarding the age of the patient. 1. Reduced revascularization potential. On a systemic level, angiogenesis is reduced by degenerative changes that occur in vessels and nerves over time [5]. In the pulp–dentin complex, age can imply a compromise of its vascular supply [6], as the size of the pulp chamber decreases due to the apposition of dentin, while calcifications tend to occur more frequently [7], as well as the apical narrowing due to the gradual apposition of dentin and cementum. 2. Changes in the functionality and potential of stem cells. Over the years, the ability of multipotent stem cells to replace damaged tissues decreases [8]. This could be related to the fact that the differentiation capacity of MSCs decreases over time, but not to the amount of inflow of MSCs into the root canal system in adults, because this amount does not change with age [9]. 3. Smaller diameter of the apical constriction in mature teeth. Currently, there is no consensus regarding the optimal size of the apical foramen for REP [4]. It should be as small as possible without affecting cell migration and reinnervation [10]. In 2007, Murray suggested that, in teeth with closed apexes, revascularization by inducing bleeding may require an apical instrumentation of 1 or 2 mm to allow the flow of bleeding [11]. Later, some authors proposed it as feasible to succeed apical diameters smaller than 1 mm [12] or equal to 0.5 mm [11].

Three key elements are essential for REPs: stem cells, scaffolds, and activators [11]. These techniques begin with the disinfection of the root canal system, followed by the induction of bleeding in the periapical region with the purpose of obtaining a blood clot. This mass would behave as a natural scaffold for the migration of undifferentiated stem cells that come from outside the apex, mostly from the alveolar bone and periodontal ligament [13], while providing growth factors that stimulate cell differentiation and proliferation, inducing the formation of new tissue.

However, the composition and concentration of the clot is unpredictable, and the uncertainty increases with age [11][14]. When bleeding is insufficient and it does not provide an ideal blood clot, an alternative material should be used. Evidence supports the use of autologous platelet concentrates [8][15][16][17], such as platelet-rich plasma (PRP) and fibrin-rich plasma (PRF) [15], which are the most popular ones. These concentrates can be used as a scaffold, by their own or in combination with a blood clot [18].

REPs' scientific evidence in adult teeth is limited. Currently, there is no specific clinical protocol for the management of these teeth. Regarding the promising future of these techniques, it is necessary to analyze the considerations that must be considered for the treatment of these teeth and the results obtained up to nowadays.

2. Development and Findings

REPs were developed to treat immature teeth of young patients. However, according to this revision and matching the results of previous systematic reviews that analyzed these treatments in mature necrotic teeth with periapical lesions [19][20], success rates obtained in adult teeth are promising. Thus, it may be possible to extend these techniques to all teeth regardless of patient's age. However, the clinical protocol for adult teeth should be different from the one for immature teeth, because of their different conditions with respect to young teeth: decreased revascularization capacity, lower potential of stem cells and, in general, smaller diameter of the apical constriction.

Regarding instrumentation, some clinicians consider that a minimal mechanical debridement is necessary to facilitate the destruction of biofilms [21], while others rely on chemical debridement using disinfectants and the use of intracanal medication to achieve the complete disinfection of the canal system [22]. From the studies reviewed, it is concluded that the majority of clinicians perform a minimal instrumentation of the canals. The instrumentation techniques and instruments used vary depending on the state of development of the tooth, predominantly reciprocating rotary instrumentation technique for the treatment of mature teeth, and manual technique with K and H files for immature teeth.

The conventional and simplest technique to achieve revascularization is by stimulating bleeding 2 mm under the apical with a manual file [23]. Previous studies have failed to achieve a consensus regarding the optimal apical diameter that better allows revascularization [4][10][11][24], although success has been reported in diameters between 0.3 to 1 mm [4]. One of the trials compares rate success through REP in mature teeth with different apical preparations (0.3 and 0.5 mm), concluding that the size of the apical diameter does not influence treatment

success [25]. Therefore, although more studies are needed, it seems that revascularization can take place in teeth with apical diameters of 0.3 mm.

Regardless the apical foramen diameter, revascularization potential may be compromised due to patient's age. Through their trials, Arslan [26] and El-Kateb [25] obtained successful results by stimulating bleeding, and most of the clinicians through case reports also performed this technique successfully. Those who did not achieve bleeding or chose platelet-rich concentrates opted for PRF, PRP, L-PRF, or the combination of both techniques.

Time-dependence relationship of pulp regeneration is one of the main challenges posed by REPs. To determine how these treatments are influenced by age, conducting randomized clinical trials in narrow age groups would be required. For example, Estefan in 2016 states that REPs can be applied in patients aged 9 to 18 years, concluding that the younger the age, the better the prognosis [10].

When an unsuccessful REP occurs in an adult patient, the cause may lie on the lower potential of its stem cells, so it is necessary to determine when it would be better to perform a cell transplant. Two authors successfully performed cell transplantations using umbilical cord mesenchymal stem cells (UC-MSCs) encapsulated in platelet-poor plasma [27] and stem cells from exfoliated deciduous human teeth (SHED) [28]. Since the immunogenicity of mesenchymal stem cells is low, cell banks may become a real alternative [29]. Although these techniques are not currently available to all clinicians, with a view to the future, Nakashima estimates that cell banks will provide stem cells cryopreserved and safely transported to the dental clinic for REP [30].

One of the main unknowns is how to determine the best combination of irrigants and intracanal medication to achieve complete disinfection of the canal system while promoting, or at least not harming, tissue regeneration. To this point, EDTA should be used in all regenerative procedures [15], as it appears to enhance the liberation of dentin growth factors [22][31][32][33], which are essential as biological inductors and remain entrapped in the dentinal matrix as reservoir [34]. Besides, EDTA partially reverses the deleterious effects of NaOCl and promotes SCAP survival and differentiation [22]. The AAE recommends an irrigation with 1.5% NaOCl (20 mL/channel, 5 min) during the first session, followed by saline or EDTA (20 mL/channel, 5 min). In adult teeth, the irrigation protocol favored by most authors in the first session is irrigation with NaOCl. Regarding the concentration, the disagreement is notorious, although most clinicians lean towards 1.5%. During the second session, there is great disagreement regarding the irrigation protocol, although most clinicians apply 17% EDTA.

It is recommended to use some activation system to maximize the viability of stem cells by achieving a bacteria-free environment. According to Castelo in 2012, continuous ultrasonic irrigation is the one that best achieves the penetration of the irrigant in lateral canals [35]. However, the possibility of extrusion into periapical tissues must be minimized. The AAE recommends negative apical aspiration for this purpose. Despite the recommendations, only two clinicians used irrigant activation devices: sonic activation [36] and negative apical aspiration [37]. Clinicians should incorporate these systems to improve canal disinfection.

As intracanal medication, the AAE recommends calcium hydroxide or a low concentration of antibiotic mixture made up of ciprofloxacin, metronidazole, and minocycline, known as triple antibiotic paste [23]. Because minocycline as an intracanal dressing may cause dentine discoloration [38], it is recommended to replace it with calcium hydroxide, double antibiotic paste composed of metronidazole and ciprofloxacin [39], or a triple antibiotic paste where minocycline is replaced with another antibiotic, either amoxicillin, clindamycin or cefaclor [13]. However, the ESE Position Statement advocates the use of calcium hydroxide instead of antibiotics, indicating that there is no evidence to support the need of using them [39]. Nevertheless, according to the literature, most dentists favor the use of triple antibiotic paste [38].

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