ISSN Print: 2394-7489
ISSN Online: 2394-7497
IJADS 2022; 8(2): 217-221

www.oraljournal.com
Received: 05-01-2022
Accepted: 09-02-2022

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Current issues in regenerative endodontics

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DOI: https://doi.org/10.22271/oral.2022.v8.i2d.1511

Abstract
Introduction: Regenerative endodontics has been defined as "a biologically based procedure designed to replace damaged structures, including dentin and root structures, as well as cells of the pulp-dentin complex."
Objective: To analyze the use of antibiotic pastes, stem cells, scaffolds and growth factors in regenerative endodontic procedures.
Methodology: PubMed, Google Scholar, SCOPUS databases were reviwed with the following keywords "Stem cells, growth factors, antibiotic paste, scaffolds".
Results: The use of antibiotic pastes based on metronidazole, minocycline and ciprofloxacin provide a suitable medium for regeneration. Factors secreted by mesenchymal stem cells can be found in the cell culture medium, called conditioned medium. Concentrated growth factor has been found to promote proliferation, migration and differentiation of SCAPs. Tissues are organized as three-dimensional structures and appropriate scaffolding is necessary to provide a spatially correct position of cell location and regulate differentiation, proliferation or metabolism of stem cells.
Conclusion: Regenerative therapy is functional as long as the patient's internal clinical conditions as well as external factors are within the required parameters to evolve correctly. Currently, biomedicine has taken a very important path in dentistry for tissue regeneration.

Keywords: Stem cells, regenerative endodontic procedure, antibiotic paste

Introduction
Regenerative endodontic procedures are planned procedures to replace damaged tissues, including dentin and root structures, as well as the cells of the pulp-dentin complex. Effective root canal sterilization is essential and antibiotics have been widely used to disinfect root canals [1]. Regenerative endodontics has been defined as "a biologically based procedure designed to replace damaged structures, including dentin and root structures, as well as cells of the pulp-dentin complex" [2]. Endogenous stem cells from induced periapical hemorrhage and scaffolds using blood clots, platelet-rich plasma or platelet-rich fibrin have been used. This approach has been described as a "paradigm shift" and is considered the first treatment option for immature teeth with pulpal necrosis. There are three outcomes of regenerative endodontic treatment; (i) resolution of clinical signs and symptoms; (ii) increased root maturation; and (iii) return of neurogenesis [3, 4]. This regenerative endodontic procedure proposes the use of a combination of antimicrobials and irrigants, no instrumentation of the canal walls, induced apical bleeding to form a blood clot and a tight seal in the root canal to promote healing [5]. Several treatment modalities have been employed to create a hard tissue barrier at the apex, including non-vital pulp therapy with calcium hydroxide, apexification with mineral trioxide aggregate, revascularization and pulp regeneration. Regenerative endodontics is a novel modality that involves the physiological replacement of damaged tooth structures such as dentin, root and pulp-dentin complex cells [6]. A non-antibiotic disinfectant approach is currently used and appears capable of providing satisfactory results for a non-vital immature permanent tooth [7]. The addition of platelet-rich fibrin is feasible and may have some advantages over MTA apexification, as it facilitates root elongation, dentinal thickening of root canal walls and narrowing of the apical foramen [8].

Currently, it has been shown that preservation in function of dental organs that meet the requirements for the evolution of a regenerative procedure are promising, provided that the initial diagnostic evaluation is correct and the selection parameters are adequate. Therefore, the aim of this article is to analyze in the literature the use of antibiotic pastes, stem cells, scaffolds and growth factors in endodontic regeneration procedures.

2. Materials and Methods

Articles on the subject published through the PubMed, SCOPUS and Google Scholar databases were analyzed, with emphasis on the last 5 years. The quality of the articles was evaluated using PRISMA guidelines, i.e., identification, review, choice and inclusion. The quality of the reviews was assessed using the measurement tool for evaluating systematic reviews (AMSTAR-2) [9]. The search was performed using Boolean logical operators AND, OR and NOT. It was realized with the words "endodontic regeneration", "Antibiotic pastes", "stem cells", "scaffolding", “growth factors”. The keywords were used individually, as well as each of them related to each other.

3. Results and Discussion

3.1 Antibiotic Pastes

Triple antibiotic paste containing metronidazole, ciprofloxacin and minocycline has been proposed as a root canal treatment drug because of its antimicrobial effects in endodontic regeneration procedures [10]. Applications of the paste vary, ranging from vital pulp therapy to the recently introduced regeneration and revascularization protocol. Studies have shown that the paste can remove microorganisms from the root canal and prepare a suitable matrix for subsequent treatments. This combination can eliminate various groups of gram-positive and gram-negative obligate and facultative bacteria, providing an environment for healing [11]. The main drawback associated with the use of minocycline is tooth discoloration. Several antibiotics have been suggested as alternatives to minocycline, such as clindamycin or amoxicillin with clavulanic acid, and it has been found that the triple antibiotic paste in combination with minocycline and amoxicillin with clavulanic acid induced more coronal discoloration compared to the clindamycin group [12]. Over periods of 1 month and 3 months, amoxicillin-clavulanate paste has no significant effect on dentin microhardness compared to double antibiotic paste [13]. The incorporation of multiple antibiotics within a nanofibrous scaffold has great potential for the development of a drug delivery system for regenerative endodontics [14]. The disinfection step with antibiotic-based pastes warrants a biocompatible strategy to promote root canal disinfection with minimal or no side effects to maximize regenerative outcomes [15]. Elimination of microbial flora in cases of immature permanent teeth with necrotic pulp is key and a challenging goal for the long-term success of regenerative therapy. The use of a polymer-based nanofiber antibiotic releaser was proposed and showed pronounced antimicrobial effects against multispecies biofilm and thus has significant clinical potential as a disinfection strategy prior to regenerative endodontics [16]. The vehicle and antibiotic formulations influenced the cytotoxicity and pH of the triple antibiotic paste. Pastes prepared with tablet or capsule and propylene glycol were less acidic and cytotoxic than those prepared with various antibiotics and H_2O [17].

The combination of antibiotics has been widely used for endodontic regeneration procedures. The use of antibiotic pastes without the use of minocycline has been implemented more to avoid dental pigmentation, this also contributes to the elimination of the microbial flora giving a good prognosis to the treatment.

3.2 Stem Cells

Regenerative endodontics is a biologically based treatment designed for immature permanent teeth with necrotic pulp to replace dentin and root structures as well as dental pulp cells. This procedure has become part of a novel modality in the therapeutic form of endodontics, and is considered as an alternative to apexification [18]. Numerous types of stem cells have been isolated from dental tissue, such as dental pulp stem cells (DPSC), stem cells isolated from human pulp of exfoliated deciduous teeth, periodontal ligament stem cells (PDLSC), stem cells of the apical papilla (SCAP) and dental follicle cells. All these cells can regenerate tooth tissue [19] which may be a good source for stem cell-based therapy in certain diseases, especially when they are considered to originate from the neural crest [20]. This broadens their applicability for tissue regeneration of both ectochymal and mesenchymal origin. The ease of tissue harvesting, high initial cell yield, low population doubling time, plasticity, multipotent capabilities and immunomodulatory properties make them suitable candidates for various therapeutic strategies. In addition, cells derived from dental tissue can be transformed into induced pluripotent stem cells to customize cell-based regenerative approaches [21]. The typical treatment for irreversibly inflamed/necrotic pulp tissue is root canal therapy. As an alternative approach, regenerative endodontics aims to regenerate dental pulp-like tissues using two possible strategies: cell transplantation and cell homing. The former requires exogenously transplanted stem cells, complex procedures and high costs; the latter employs endogenous host cells to achieve tissue repair/regeneration, which is more clinically translatable [22, 23]. Indeed, pulp mesenchymal stem cells, including postnatal dental pulp stem cells (from permanent teeth) and human exfoliated deciduous tooth stem cells, possess unique properties based on their origins from neural crest or glial cells. In addition, they reside in a neurovascular niche and have the potential for neurogenesis, angiogenesis and neurovascular inducing activity [24]. The role played by these cells in the repair process is mainly attributed to paracrine mechanisms mediated by their secreted factors, namely the secretome. The secreted factors can be found in cell culture medium, called conditioned medium. In addition, conditioned medium has many advantages compared to cells, such as its potential use in allogeneic therapies [25].

In the past, cells used to be isolated only from bone marrow, nowadays it has been demonstrated that the dental organ releases from itself a myriad of mesenchymal stem cells capable of differentiating and proliferating for successful regenerative endodontic procedures, such as SCAPs, DPSCs and others.

3.3 Scaffolding

Tissues are organized as three-dimensional structures and appropriate scaffolding is necessary to provide spatially correct positioning of cellular location and to regulate differentiation, proliferation or metabolism of stem cells [26]. The formation of blood clots as scaffolds in the apical third of the root canal system has been shown to promote further root development and reinforcement of the dentin walls by deposition of mineralized tissue, resulting in an advancement from traditional apexification procedures to regenerative endodontic treatment for immature non-vital permanent teeth [27]. Regenerative endodontic procedures involve disinfection of the root canal system without damaging the endogenous stem cell potential present in the apical papilla and other tissues. These stem cells are introduced into the root canal space by inducing a blood clot followed by placement of an intracanal barrier to prevent microleakage [28]. Among the ideal requirements of a scaffold: high porosity and adequate pore size are needed to facilitate cell seeding and diffusion throughout the structure for both cells and nutrients; it must allow efficient transport of nutrients, oxygen and waste; biodegradability is essential, as surrounding tissues must absorb the scaffolds without the need for surgical removal; the rate at which degradation occurs must match the rate of tissue formation; it must be biocompatible; and it must have adequate physical and mechanical strength [26]. Platelet-rich plasma (PRP), a first-generation autologous platelet concentrate with a rich source of growth factors, has been proposed as a possible substitute appendage/scaffold [29]. It is easy to prepare, rich in growth factors and forms a 3D fibrin matrix that helps to trap growth factors. The concentration of platelets in PRP exceeds 1 million/mL, which is 5 times more than the normal platelet count [30]. A higher platelet count increases the amount of growth factors secreted by platelets, which helps stem cell proliferation to induce tissue healing and regeneration [31]. Platelet-rich plasma, platelet-rich fibrin and platelet sediment can produce similar clinical and radiographic results to induced blot clot without the need for prior apical hemorrhage and with significantly less tendency for root canal obliteration. Radiographic root area and radiographic canal area may reveal minor differences that cannot be determined by linear measurements [32].

Regeneration in endodontics requires adequate disinfection, but the use of scaffolds is indispensable as it functions as a means of cell adhesion. Platelet-rich plasma has functional growth factors, the production of a clot internal to the root canal by the same operator is also adequate for the follow-up of the procedure.

3.4 Growth Factors

Concentrated growth factor (CGF) is considered a natural biomaterial that is better than platelet-rich fibrin (PRF) in bone regeneration, but there is little information acquired in regenerative endodontics [33]. Angiogenesis is a key factor in tissue regeneration, but the role of CGF in vessel formation is unclear [34]. The biological effects of CGF on human apical papilla stem cells (APSCs); including cell proliferation, cell migration, mineralized nodule formation and gene expression of alkaline phosphatase, dentin sialophosphoprotein (DSPP) and dentin matrix protein (DMP)-1 have been investigated and quantified. Thus, concentrated growth factor has been found to promote the proliferation, migration and differentiation of SCAP and could be a promising biomaterial applied in regenerative endodontics [35]. CGF has a positive effect on the proliferation, migration and differentiation of hDPSCs exposed to LPS *in vitro*, and can also promote the regeneration of the dentin-pulp complex of immature teeth in beagle dogs *in vivo* [36]. Concentrated growth factor is a promising scaffold for the treatment of dentin-pulp complex disorders. Given its characteristics of autogenesis, convenience, usability and biodegradability, concentrated growth factor has gained popularity in the medical and dental fields for repairing bone defects and promoting soft tissue healing. Numerous *in vitro* studies have shown that concentrated growth factor can promote the proliferation and migration of dental stem cells [37]. CGF is a promising regenerative material that serves as a scaffold and adjunctive growth factor for tissue engineering. The host immune response, in particular macrophage activity, plays a critical role in injury repair and tissue regeneration. However, the biological effect of CGF on the immune response is unclear [38]. The combination of CGF with stem cells and biomaterials significantly improves bone regeneration and the effect of allograft or collagen membrane is better than CGF alone. For a better examination of the biological results of CGF, standardization of CGF preparation with respect to the choice of test tube material for blood collection, the required blood volume, the necessary platelet count in FGC and the most appropriate type of CGF, are recommended [39]. Transforming growth factor beta 1 (TGF-β1) is a key morphogen in regenerative endodontics that is deposited in peritubular dentin. It should be possible to release this molecule in regenerative endodontic procedures of both mature young roots and immature roots [40, 41].

The concentrated growth factor will provide the signaling function for tissue engineering to have its place and function correctly in regenerative endodontic treatment, it acts correctly providing good autogenesis as it promotes repair.

4. Conclusions

Triple antibiotic paste containing metronidazole, ciprofloxacin, and minocycline has been proposed as a drug for root canal treatment because of its antimicrobial effects. Cells derived from dental tissue can be transformed into induced pluripotent stem cells to personalize cell-based regenerative approaches. Platelet-rich plasma, a first-generation autologous platelet concentrate with a rich source of growth factors, has been proposed as a potential appendage/substitute scaffold. Concentrated growth factor is a promising regenerative material that serves as a scaffold and growth factor adjunct for tissue engineering. The host immune response, in particular macrophage activity, plays a critical role in injury repair and tissue regeneration.

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