

Review Article

Current Trends in Pulp Regeneration-Review

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Abstract

Advances in knowledge and treatment options have made pulp regeneration a current objective in clinical dental practice. In recent years, several studies have been carried out and there have been several attempts to develop methodologies regarding pulp regeneration.

For the survival as well as for the long-term preservation of the tooth, obtaining a solid and viable pulp is essential. Current endodontic treatment concepts are based on replacing the inflamed/necrotic pulp tissue with a synthetic biomaterial. Recent studies have proposed total or partial pulp regeneration as an alternative treatment method.

Recent studies have highlighted that inflamed/necrotic pulp tissues can be replaced by regenerated pulp tissues. Thus, the quality of life is improved through regenerative endodontics. Teeth are revitalized. The latest researches on pulp revascularization have indicated by clinical and radiographic results a possible clinical application of pulp regeneration using the modern cellular homing strategy. Thus, pulp tissues that are functional must be clinically regenerated with the characterization of vascularization, with the characterization of reinnervation as well as with a dentin deposition having a regulated rate almost similar to the normal one. The purpose of this review is to evaluate current pulp treatment options through regenerative approaches.

Keywords: Endodontic Treatment; Progress; Alternative Treatment; Total or Partial Polar Regeneration

Introduction

In recent decades, dentistry has seen great advances in treatment options involving tissue engineering. Among the areas that benefit from these advances, endodontics stands out through remarkable developments regarding the widening of the range of concepts and treatment options [1]. Many discussions regarding the importance of restoring the pulp-dentin complex fall into this context. Schmaltz, et al., demonstrated that continued root formation should be encouraged using the administration of vital pulp therapy [1]. The literature provides several good examples of current treatment strategies [2]. These can be effective. On the other hand, the prospect of obtaining a full recovery of dental functions is extremely attractive. Regenerative endodontics has gained much attention in the past decade. It has gained attention because it offers an alternative approach to tooth treatment. The objective of regeneration is to obtain tissue and restore function to its original state [3].

A clinical protocol has been developed for pulp regeneration. This protocol intends to restore the pulp/dentin tissues in the root canal space (revitalization/revascularization) [4]. Histological studies in animals and humans have shown that pulp regeneration by revitalization is difficult to achieve [5,6]. They demonstrated that in tissue engineering there is cell-based tissue regeneration and cell-free tissue regeneration. Cell-based regeneration involves the transplantation of exogenous cells into the host. Revitalization belongs to regeneration that is not based on cells [7-12]. Recent studies have shown that the cell-based approach regenerates pulp/dentin but has a number of limitations [13-15]. The purpose of this article is to review current pulp treatment options through regenerative approaches.

Recent Advances in Pulp Regeneration

In 2020, Schmalz and colleagues used as research methods the study of clinical success rates in classical treatments. They studied pulpotomy/root canal obturation after pulpectomy/removal of necrotic tissue. The results were compared with the latest reports on regenerative approaches (revitalization, partial/total pulp regeneration) [1-15]. The results of the study highlighted the fact that there still remains an additional treatment option to the placement of an apical plug, a revitalization of immature teeth with pulp necrosis. This leads to clinically acceptable results but still with low predictability regarding final root formation. Coronal regeneration of amputated pulp in immature teeth is today a promising scientific approach. Unfortunately, there is a lack of data from clinical trials. In the case of mature teeth, we encounter a reduced regeneration potential [1].

Unfortunately, regenerative procedures using cell transplantation or cell homing are mainly in the experimental phase. There are only two clinical trials on cell transplantation. Schmalz proposes revising the classification of pulp diseases in parallel with the development of regenerative therapies. It proposes the improvement of diagnostic tools [1].

Ribeiro, et al., performed a critical evaluation of alternative antimicrobial strategies used in place of the traditional Triple Antibiotic Paste (TAP). Ribeiro's review used databases found on PubMed/Medline, LILACS, Embase, Web of Science, BVS, Scopus, SciELO and Cochrane Library. Clinical studies (*in-vitro/in-vivo/in-situ*) were selected. Antimicrobial alternatives have been evaluated for regenerative endodontics at TAP. In the evaluation, studies without an experimental TAP group were eliminated. The results of the study revealed that most of the alternative agents performed similarly to TAP [16].

The study by Eramo, et al., demonstrated that an alternative approach can be used for the typical treatment of irreversible inflamed/necrotic pulp tissue treated by root canal treatment. Thus, regenerative endodontics, as an alternative approach, proposes the regeneration of dental pulp-like tissues by using two strategies: cell transplantation as well as cell localization. Cell transplantation required exogenously transplanted stem cells. It requires complex procedures and high costs. Uses endogenous host cells in tissue repair/regeneration. These can be clinically transplanted. The results of Eramo's study reflect or systematic review of cell localization examinations for dental pulp regeneration from many articles on *in-vitro* experiments, *in situ* pulpal revascularization, *in-vivo* ectopic transplantation models (MEDLINE/PubMed and Scopus databases). *In-vitro* studies have shown that multiple cytokines have the ability to induce migration as well as proliferation and differentiation of dental pulp stem/progenitor cells. *In-vivo* studies revealed that regenerated connective pulp-like tissues with neovascularization were obtained. *In-situ* pulp revascularization studies regenerated intracanal pulp-like tissues with neovascularization, innervation, and dentin formation. However, further research is still needed for a better understanding, a reliable and effective approach in endodontics. Despite all these shortcomings, cell localization is present in the most viable clinical modality for dental pulp regeneration [17].

Austah, et al., studied pulp-dentin complex regeneration as the penultimate goal of Regenerative Endodontic Procedures (REP). Histological results obtained by Austah demonstrated the formation of reparative tissue in human teeth that were extracted post-REP. The lack of precise characterization did not allow identifying the true nature of the tissues formed post-REP. However, Austah's study remains the first study to demonstrate a recapitulation of several tissues usually found as part of a pulp-dentin complex in teeth treated with REP [18].

Duncan and Cooper demonstrated that improving Regenerative Endodontic Procedures (REP) requires an understanding of key clinical questions [19]. This understanding must be combined with a biological knowledge of the behavior of dental tissues normally, during disease and during treatment. Duncan and Cooper believe that partnerships between clinicians and researchers

are essential for further developments [19].

The study by Duncan and Cooper provided a pertinent framework for the biology of the dentin pulp as well as the interplay between infection, inflammation and regeneration. It highlighted that the release of Neutrophil Extracellular Traps (NETs) in the pulp is intended to limit bacterial infection, but carries the risk of exacerbating cell death and chronic inflammation. High levels of these structures may be determined by the host's immunological processes being ineffective. They can be caused by viral infections. Duncan and Cooper postulated a proinflammatory link in the pulp. The connection is between NETs and the inflammasome that is activated by the molecular patterns associated with the pathogen and the molecular patterns associated with the lesions [19].

Bertassoni conducted a study on dental pulp [20]. The dental pulp is a highly vascularized and innervated tissue. It is a very biologically active test. Previous studies have shown that the vasculature of the dental pulp is a vital requirement for the functional performance of the tooth. Controlled regeneration of the dental pulp vasculature constitutes a challenge for regeneration efforts in endodontics [21].

Bertassoni in his study addressed recent advances and challenges regarding the use of microengineering methods as well as biomaterial scaffolds used in the fabrication of the vascular microenvironment of the dental pulp. He studied the conditions necessary to control the growth and differentiation of vascular capillaries. He studied the conditions necessary for the formation of stable mature pericyte-supported microvascular networks in three-dimensional hydrogels as well as in fabricated microchannels. Recent biofabrication methods (three-dimensional bioprinting, micromolding) were discussed. The study provided new research directions in the field regarding clinical and translational strategies in regenerative endodontics, focusing on dental pulp vasculature [20].

Nageh, et al., evaluated the possibility of regaining pulp sensitivity in mature necrotic teeth using modified regenerative endodontic procedures [22]. Regenerative endodontic procedures have been modified by inducing bleeding in root canals as well as using Platelet-Rich Fibrin (PRF). The study included 15 patients with necrotic pulp (symptomatic/asymptomatic apical periodontitis). The results of the study showed that the presence of tenderness indicates the formation of vital pulp tissue. The study highlighted that the restoration of actual pulp tissue following regenerative endodontic treatment is still debatable. More evidence from large-scale investigations is needed [22].

Yang, et al., provided a detailed overview of current regenerative endodontic approaches for tooth revitalization. Yang's study focused on the necessary prerequisites, including root canal disinfection as well as widening of the apical foramen. The study focused on cell migration strategies in pulp regeneration. During pulp inflammation, the pulp space is invaded by various microorganisms of oral and/or food origin that form a biofilm on the canal walls. It infiltrates into the dentinal tubules. Root canal disinfection for pulp regeneration is essential (EndoVac apical negative pressure irrigation system, intracanal antibiotic medication, ultrasound-assisted irrigation, laser irradiation, etc.) [23].

Adequate size of the apical foramen is another indispensable precondition for pulpal regeneration (especially in mature teeth with closed apex in adults). The root apex is reduced during tooth root development. Finally, it closes. It forms a narrow foramen. The foramen is the only access through which the blood vessels, nerves and cells inside the dental pulp communicate with the surrounding tissues. If the apical foramen is too small, it does not allow adequate pulpal revascularization in reimplanted permanent incisors. A wider apical foramen (> 1 mm) removes most of the dentin from the apex leading to apical trauma/fracture. Thus, the peak should be as small as possible. It should not affect cell migration. It should not affect neovascularization and reinnervation [24].

The regenerated tissues must be connective tissues that produce new dentin at a controlled rate similar to the normal pulp, present a cell density and architecture similar to the natural pulp, be vascularized and innervated [25]. In general, the functional characters of the regenerated tissues are more important characters than the morphological characters. Along with dentinogenesis, vascularization and innervation are characteristics of the pulp. The regenerated blood vessels must have a connection with the periapical tissues. The regenerated tissue must be innervated for the teeth to be able to sense heat/cold

stimuli. Teeth must be able to feel pain during infection [26]. Studies to date have examined dentin deposition and vascularization of regenerated tissue [26].

Pagella and colleagues, focused on tissue reinnervation, used microfluidic co-culture systems in the study of dental innervation. The results of the study demonstrated that microfluidic co-culture systems provide a viable tool in investigating innervation in developing or regenerating teeth. As a result, such systems can be used to analyze the innervation of the regenerated dental pulp [27]. Pulp regeneration can be achieved by cell transplantation strategy and cell displacement strategy. Compared to the cell transplantation strategy, a cell displacement strategy can be performed clinically more easily. There is no need to isolate/manipulate stem cells *in-vitro* [28]. Compared to pulp revascularization in the case of immature teeth, the cellular homing strategy was introduced and applied in pulp regeneration. [21].

Stem cell sources are a major concern for pulp regeneration by cell localization strategy. Possible sources of cells used in pulp regeneration by cell homing include Dental Pulp Stem Cells (DPSC), Bone Marrow Stem Cells (BMSC), Apical Papilla Stem Cells (SCAP), etc [29,30]. Studies by Mitsiadis have shown that for severely damaged/carious teeth, stem cells residing in the dental pulp are responsible for the repair and/or regeneration of damaged dental tissues. Some viable DPSCs may reside in the root canal system [29,30]. DPSCs (DPSCs-IPs) were identified from the inflamed dental pulp. Studies have demonstrated that there are similar properties of mesenchymal stem cells to those of Normal Pulp cells (DPSCs-NPs) [7]. It is very difficult to obtain DPSCs-IPs in mature teeth, this after mechanical preparation as well as after root canal disinfection. Thus, residual DPSCs in the canal may contribute to pulp regeneration in immature teeth [29,30].

Recent studies on the cellular sources of pulp regeneration using the cellular homing strategy may reveal many insights into molecular signaling selection. Thus, the appropriate signaling molecules used in pulp regeneration facilitate the recruitment of stem cells with vasculogenic and neurogenic differentiation potential. At the same time, it inhibits cells with osteogenic/cementogenic potential. An example is the cells of the periodontal ligament [31,32]. Although some recent experimental and clinical studies have demonstrated the formation of vascularized pulp-like tissues, not enough is known about the function of the regenerated tissue. Therefore, experimental and clinical studies are still needed to obtain a functional pulp regeneration [33]. Cell transplantation and cell transfer are current innovative scientific approaches. However, the active recruitment of stem cells (endogenous progenitors) from root canals in order to regenerate pulp tissues is still a new concept. This new concept may provide a viable opportunity for clinical application of current biologically based therapies. It constitutes a viable opportunity for pulp regeneration [31].

In the case of the application of endodontic treatment through cellular hoing, three clinical procedures must be performed: the disinfection of the root canal simultaneously with the widening of the apical foramen; bioactive skeleton transplantation made with signaling molecules as well as tooth restoration; periodic monitoring of the viability (neovascularization and reinnervation) of the regenerated pulp. Further experimental and clinical studies are needed to realize the clinical translation of pulp regeneration when using the cellular homing strategy. New experimental and clinical studies on root canal disinfection, use of intracanal medication is still needed. Further experimental and clinical studies on assisted irrigation with the EndoVac apical negative pressure system are still needed. Further experimental and clinical studies on ultrasound and laser irradiation are needed. Further experimental and clinical studies on antibacterial efficacy are still needed. Further experimental and clinical studies on the effects on cell viability as well as the mechanical strength of dentin for each method or combinations of methods are still needed [33,34].

Conclusion

Although the feasibility of dental regeneration has been demonstrated in some clinical studies, the predictability is still low. In pulp regeneration some strategies appear to be more promising than others. Attention should be paid to clinical scenarios for the effective development of partial or total treatment in pulp regeneration. In terms of complete elimination of microorganisms, TAP remains an excellent option. Determining the appropriate size of the apical foramen remains to be investigated. In order not to affect cell migration as well as the formation of blood vessels and nerves in pulp regeneration, the size of the apical foramen should be as small as possible. Selection of the appropriate combination of scaffold and growth factors remains to be investigated.

Contribution Note

All the authors equally contributed to the drawing up of the present paper.

Conflict of Interest

The authors have no conflict of interest to declare.

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