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Regenerative Endodontics and Its Application in the Treatment of Mature Permanent Teeth - A Review

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Abstract: ***Regenerative endodontics can be a useful alternative to conventional endodontic treatment in mature teeth with necrosis/apical periodontitis. This review spans articles in PubMed, Web of Science and Scopus. It examines the biological considerations when applying revitalization techniques in adults and the clinical reports on treatment outcomes. Regenerative procedures used in pediatric dentistry could be successfully implemented, with some modifications in the clinical protocol, in order to meet the specific conditions such as: small apical foramen, less blood supply and decreased amount of growth factors. Additional research is required to establish the optimum conditions that can contribute to a successful treatment.***

Keywords: Regenerative endodontics, revitalization, revascularization, mature permanent teeth, stem cells

1. Introduction

The various aspects of tooth regeneration have been the focus of numerous studies in recent years. While the aim of dentistry as a whole has always been to preserve the form, esthetics and function of the tooth, scientists have strived towards finding ways to restore the lost vitality of the tooth. In 2001, regenerative endodontics emerged in the field of pediatric dentistry with the introduction of the term "revascularization" for the treatment of immature permanent teeth with apical periodontitis [1].

The term "revitalization" was proposed by Huang & Lin since the process involves not only the formation of blood vessels, but hard dental tissues as well [2]. "Regenerative endodontics" was adopted by the AAE (Murray et al. 2007), turning the focus on the tissue engineering that is carried out in the procedure [3]. All of those terms – revascularization, revitalization and regenerative endodontics are used interchangeably in the literature. However, in most cases, the use of regenerative techniques is limited to the revitalization of the dental pulp and root development of immature permanent teeth [4].

Recently, the focus of researchers has turned towards applying these techniques in the treatment of mature necrotic teeth in adult patients, thus broadening the scope of scientific innovation and research. Endodontic treatment is a complicated lengthy procedure, often involving several visits and considerable costs for both the patient and the dental practitioner. Endodontically treated teeth are more susceptible to future complications like flare-ups and fractures. A meta-analysis of 63 studies encompassing the years between 1922 and 2002 showed that successful outcomes after endodontic treatment have not significantly improved over the years, despite the introduction of new techniques and materials for root canal preparation, medication and obturation [5].

Furthermore, the majority of endodontic cases are still treated by a general practitioner who in term affects their prognosis. Therefore, a change in the concept of endodontic treatment is needed and the field of regenerative endodontics shows great promise. It is generally recognized that some bacteria manage to survive in the endodontic space after treatment [6].

On the other hand, the regeneration of the dental pulp and blood vessels within the root canal space offers the potential of activating the immune system. This involves the migration of lymphocytes and macrophages that can eliminate the residual infection [7]. This could lower the incidence of flare-ups. Moreover, the regenerated tissues might be more fracture resistant than traditionally endodontically treated teeth [8].

2. Literature Survey

Before the implementation of the revascularization technique for immature permanent teeth, apexification with calcium hydroxide was the treatment of choice, later followed by the introduction of the MTA plug in order to encourage the formation of an apical barrier [9].Both of these techniques produced reliable results with favourable clinical outcomes [10-12]. Since the application of calcium hydroxide is a lengthy procedure that involves several visits, the MTA plug has become more popular as it significantly reduces chair time. On the other hand, they cannot induce root maturation, thus leaving the root formation incomplete. This led to the introduction of the revitalization techniques as early as 1971 [13]. Nygaard-Ostby & Hjordal caused bleeding from the periapical area in both previously vital and non-vital teeth. The histological examination of the teeth after up to 3 years showed the formation of connective tissue and cementum in the teeth that were vital prior to the procedure, but not in those with necrotic pulp. The first application of the technique in non-vital teeth was carried out by Iwaya et al., based on previous studies involving

revascularization of dog's teeth [1, 14]. This was later followed by a protocol for revascularization proposed by Banchs & Trope, adding minocycline to the antibiotic mixture used by Iwaya et al., thus establishing the use of the triple antibiotic paste [15]. MTA was used as a barrier between the blood clot and the coronal part of the tooth. In 2018, the American Association of Endodontists (AAE) issued the revised clinical considerations for a regenerative procedure [16]. Nevertheless, they are still limited to the field of pediatric dentistry and used for treatment of immature permanent teeth.

3. Problem Definition

The aim of the present review was to explore the possibilities of applying regenerative techniques in mature permanent teeth by providing a comprehensive view on the current available literature.

4. Methodology / Approach

This review of the literature was performed using the platforms PubMed, Web of Science and Scopus. The keywords used were "revitalization", "revascularization", "regenerative endodontics", "mature permanent teeth", "adult patients". The database search covered original articles, reviews, comparative studies and textbooks published since the 1980s to the present day. The main focus was on the innovations of the last decade, their application and future prospects in the treatment of adult patients.

5. Results / Discussion

At present, there are two promising strategies for translating regenerative techniques into the field of adult endodontics:

1) Cell transplantation of ex vivo cultivated stem/progenitor cells;
2) Cell homing by molecules that recruit the patient's resident cells.

The sources for cultivation of stem cells in adults can be numerous:

1) Bone marrow-derived multipotent stem cells (MSCs) (BMSCs);
2) Dental pulp stem cells (DPSCs);
3) Stem cells from human exfoliated deciduous teeth (SHED);
4) Periodontal ligament stem cells (PDLSCs);
5) Dental follicle stem cells (DFSCs);
6) Tooth germ progenitor cells (TGPCs);
7) Stem cells from the apical papilla (SCAP);
8) Oral epithelial progenitor/stem cells (OESCs);
9) Gingiva-derived MSCs;
10) Periosteum-derived stem cells (PSCs);
11) Salivary gland-derived stem cells (SGSCs) [17].

BMSCs can be harvested from orofacial bones during dental surgical procedures (extractions, implants, cysts removal). Studies have shown that these cells have a promising capacity for proliferation and differentiation [18, 19]. However, the amount of cells that can be harvested is very little and must involve a surgical procedure that may not be warranted for a routine endodontic treatment. DPSCs are collected from dental pulp itself and thus show a natural tendency to differentiate into secondary odontoblasts and form reparative dentin [20]. Like SHEDs, they are reported to have multi-differentiation and self-renewal properties, but both types of cells have no availability in an adult dentition – DPSCs are removed during endodontic treatment with pulp extirpation, and SHEDs belong to the deciduous dentition [21, 22]. The OESCs can only differentiate into epithelial cells, which limits their usage to mucosal grafts [23].PSCs have shown a high potential in bone regeneration and implantology [24]. One study has shown that MSC-slike cells isolated from the salivary glands could be differentiated into adipogenic, osteogenic and chondrogenic cells [25].PLSCs are known to be a source of progenitor cells to form new fibroblasts, osteoblasts and cementoblasts and therefore could be considered a valuable target in future treatments [26].

On the whole, the stem cells future research could focus on must be easily accessible in order to be implemented into routine endodontic practices and must have the right potential for differentiation. Of all the cells listed above, researchers have focused on alveolar bone stem cells, PDLSCs and any other cells that can be found in the periapical area of the tooth [27].

However, cell transplantation of ex vivo cultivated stem/progenitor cells is a lengthy and complicated method that is difficult to implement into everyday practice. Focus has now shifted onto a process called cell homing that eliminates the need to harvest the stem cells from their original location but instead migrates them into the root canal system with the help of appropriate stimuli. This involves two distinct steps – the migration, also known as "cell recruitment" and the subsequent differentiation of the cells into odontoblasts, fibroblasts and other dental pulp cells. This is encouraged by the application of a variety of growth factors. The method first described by Kim et al. [28]. They used extracted mature permanent teeth. After sterilization and removal of any organic components in the root canal system, the researchers inserted a collagen scaffold into the root canals, in a combination of growth factors (platelet-derived, fibroblast-related, vascular endothelial, nerve growth factors and bone morphogenetic proteins). The teeth were implanted in rats for up to 6 weeks – pulp-like tissue with blood vessels was found upon examination. Additionally, the soft tissue was subjected to an enzyme-linked immunosorbent assay that indicated the presence of blood vessels, nerve-like fibers and dentin-like structures [28].

An interesting clinical study was conducted by Arslan et al. [29]. They treated 58 patients equally distributed into 2 groups – first group underwent conventional root canal treatment and the second group was subjected to regenerative endodontic procedures. All cases presented with radioluscent periapical lesions. The clinical protocol for the second group included the use of the triple antibiotic paste (doxycycline, metronidazole, ciprofloxacin) for 3 weeks, followed by inducing bleeding into the root canal, blood clot formation and placement of MTA to seal the root

canal 3 mm below the cementoenamel junction. Interestingly, they did not use any additional growth factors and relied solely on those coming with the bleeding from the apical area. In the 1-year follow up 50% of the teeth that underwent regenerative endodontic procedures had a positive response to electrical pulp testing. This cannot be used as a sole indicator for regeneration of pulp tissue but is one of the requirements described by Law and used as a guide in these procedures [30]. Similar findings were reported by Paryani et Kim in a report of 2 cases of periapical lesions that showed resolution of the apical radiolucency and no clinical symptoms at follow up [31].

In order to consider a pulp regeneration procedure successful, a pulp-dentin complex must be formed, which includes the presence of blood vessels, odontoblast layer and nerve fibers. Histological examination of immature permanent teeth has showed the presence of pulp-like connective tissue, which included those structures with the exception of mature nerve fibers [32]. Similar results were reported in a recent animal study, irrespective of the scaffolds used. [33]. In a clinical case report, Arslan et al. were able to perform a histological evaluation of the central incisors of a 20-year-old girl with apical periodontitis [34]. Again, they found fibrous connective tissue, bone-like tissue and vascular structures.
As a whole, the reports about the histological structure of the pulp-like tissue found in revitalized mature permanent teeth are scarce. Nevertheless, they do not show any significant differences from what has been observed in immature permanent teeth [35].

Revitalization techniques in permanent mature teeth with necrosis and/or apical periodontitis present a challenge because clinicians cannot rely on the abundance of growth factors typically found around the apex of a tooth with vital, but inflamed pulp. The targeted teeth are necrotic and/or have periodontal lesions, which hinders the healing process. Additionally, these are teeth with mature apices and, therefore, the flow of blood and potential growth factors from the apical area is limited. These problems could be addressed by modifying the following factors: the enlargement of the root canal, the antibiotic combinations used, the concentration of NaOCL used for irrigation, the duration for which the antibiotic paste stays inside the tooth. For example, even though studies show what 1-2 days of antibiotic paste treatment could be sufficient for disinfection, given the specifics of mature necrotic teeth, this duration might be increased for up to several weeks [36-38]. The suggested concentration of NaOCL ranges between 1-6% [39]. Studies have shown that higher concentrations of NaOCl can destroy SCAP cells and limit their differentiation potential [40]. On the other hand, in mature permanent teeth with necrosis/apical periodontitis the microbial load in the root canal system is much higher than that in an inflamed pulp of an immature tooth. Therefore, further investigation is required in order to establish the optimum concentration in those particular cases. Another important factor for the success of the treatment could be the extent to which the root canal is prepared, reflecting on the amount of necrotic dentin that needs to be removed, as well as the diameter of the prepared apical foramen. Arslan et al. suggested enlargement of the root canal 5 to 6 times larger than the first binding file in order to eliminate any residual bacteria and ensure a high success rate. Another study investigated healing in relation to the preparation method used [41]. They found out that success cases were 48%, 72%, 80%, 85% and 92% when the canals were prepared 2, 3, 4, 5 and 6 sizes larger than the first binding file.

There is no sufficient information available in the literature about what the best clinical protocol in the case of mature necrotic teeth is and thus further research in this area is required. Nevertheless, initial reports show promising results similar to those achieved in immature permanent teeth.

6. Conclusion

In conclusion, the reports so far indicate that the principles of regenerative endodontics could be successfully applied in the treatment of mature permanent teeth with apical periodontitis/necrosis, leading to an absence of clinical signs and symptoms and resolution of the apical translucencies.

7. Future Scope

Some modifications in the clinical protocol might be required in order to overcome the difficulties of managing teeth with a fully developed apex and necrotic pulp. Furthermore, new diagnostic tools for the detection of the formation of a true pulp-dentin complex must be introduced. So far, clinicians rely only on radiographic findings and clinical symptoms, which is not sufficient in assessing what kind of tissue has been formed in the root canal space.

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