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Current and future options for dental pulp regeneration

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Abstract
Introduction: Pulp regeneration is a successful biological procedure to replace structures that may be damaged in the tooth, including the root and pulpodentinal complex.
Objective: To evaluate the literature on pulp regeneration and its implication within the biological principles of regeneration, as well as its repair and disinfection of the dentin-pulp complex, current methods in pulp regeneration and their limitations and future of regenerative therapy.
Methodology: In this study the search codes were: pulp regeneration in conjunction with endodontics, objective, treatment, methods. The search for articles was performed in PubMed, Google Scholar and Scopus databases.
Results: Pulp regeneration seeks to restore pulp function as well as regenerate the tissues surrounding the tooth, consider future complications that could bring this type of treatment will be given by the inability of the formation of osteocementoid tissue, the treatment for regeneration that has greater efficacy for the elimination of infection is irrigation with the help of EDTA followed by NaOCl, Mechanized debridement has also proven to be a crucial step in this treatment, one of the new methods is the use of stem cells since it has been observed that they help in the neurovascularization of the pulp, so a complete formation of the root is expected although there may be risks such as obliteration of the canal or dental ankylosis.
Conclusions: Pulp regeneration is a tool that nowadays grants a good success rate, so it has been implemented as a first option treatment in cases of some infection or trauma of the tooth with incomplete development.

Keywords: Pulp regeneration, methods, endodontics, diagnosis, treatment

1. Introduction
Tooth loss or tissue destruction leaves wounds to which the organism reacts differently, and its response depends on the extent of the damage, the functional impairment and the biological potential of the organism [1]. Regenerative endodontics is a valuable tool that leads to the physiological replacement of damaged tooth structures such as dentin, root and pulp-dentin complex cells [2].
The challenge of endodontic regeneration is determined by clinical conditions that determine five types of tissue requirements: pulp connective tissue formation, dentin formation, revascularization, reinnervation and root edification [3]. A wide range of biomaterials and scaffolds, genes, stem cells and growth factors have been used by various researchers to apply new approaches to pulp tissue repair [4].
So one of the main priorities is the repair of oral and maxillofacial functionalities and esthetics for patients affected by tooth loss, congenital defects, trauma deformities or various dental diseases [5].
There is no adequate analysis of pulp regeneration on certain relevant points such as the different techniques that have been used for its treatment, which is why in this research an analysis of functional pulp regeneration as an alternative treatment of immature permanent teeth for their apicoformation was carried out. The objective of this review is to analyze the literature on the objective of pulp regeneration, treatment, new methods for regeneration, the future and limitations of pulp regeneration.

2. Materials and Methods

Information from articles published in PubMed, SCOPUS and Google Scholar was analyzed with emphasis on the last 5 years. The quality of the articles was analyzed based on the standard guidelines, i.e., identification, review, choice, and inclusion [6]. The quality of the review was assessed using the measurement instrument for evaluating systemic reviews. The search was performed using Boolean logical operators AND, OR and NOT. It was realized with the words "Pulp regeneration", along with the following terms: "treatment", "methods", "future" and "limitations", also in conjunction with logical Boolean operators OR y AND.

3. Results and Discussion

3.1 Biological principles of regeneration

3.1.1 Regenerative medicine

Regenerative medicine is an area that encompasses cellular and molecular biology, materials science and bioengineering to regenerate, repair or replace tissues [7], combining the principles of tissue engineering and self-healing in the regeneration of cells, tissues and organs to restore their primary function [8]. The previous decade saw the emergence of this new field that strives to offer a substitute for maxillofacial reconstruction, to complement the treatment goals for reconstruction/regeneration of the oral and craniofacial complex, which includes teeth, periodontium, bone, soft tissues (oral mucosa, conjunctiva, skin as well as blood vessels, muscles, tendons and nerves) [9].

3.1.2 Regenerative pulp therapy

Regenerative endodontic therapy means the physiological replacement of damaged pulp tissue and achieving functional recovery of the dentin-pulp complex [10]. So the main objective of regenerative endodontics is that through its treatment to be able to restore the function of the normal pulp as well as its repair and senility referred to necrotic and infected teeth with incomplete roots, which would result in the restoration of the protective functions [11] as this type of teeth that have not completed their root development leads to teeth with very short root, roots with very thin walls and an inadequate crown-root relationship [12], there are other objectives or results within regeneration such as better root maturation, resolution of signs and symptoms, return of neurogenesis [13] and healing of periapical lesions [14].

3.1.3 Procedures

Regenerative endodontic procedures that have the potential to be used for this type of cases [15] have evolved rapidly in the last two decades and are widely used in clinical endodontics [16]. There are different procedures that have been employed such as tissue engineering using stem cells, biomimetic scaffolds and growth factors to help regenerate pulp tissue damaged by bacterial infection, injury or developmental defects [17]. Today's advances in regenerative endodontic treatment are giving a better understanding and outcome using stem cells for repair of the damaged pulp-dentin complex [18].
Consider future complications that may arise from this type of treatment will be due to the inability to access the canal due to the formation of osteocementoid tissue.

3.2 Repair and disinfection of the dentin-pulp complex

3.2.1 Use of anesthetics and bioceramics in pulp regenerative therapy

It has been shown that endodontic regenerative techniques appear to be superior to apexification techniques in terms of aiding root maturation, i.e., root wall thickening and root elongation [19]. Physicians should first consider the use of a non-vasoconstrictive anesthetic when attempting to induce bleeding, the use of a collagen matrix is useful for controlled placement of MTA at a desired and optimal level, although consideration should be given to reporting the potential for staining, especially in anterior teeth when the triple antibiotic paste contains minocycline [20].

3.2.2 Application of irrigants

Disinfection inside the canal is a very important step in regenerative endodontic procedures, within the materials to irrigate is EDTA 17% that helps for better cell survival[21]; and it has been studied that it helps the growth factors to be released directly from the dentin through conditioning with EDTA [22], followed by 1.5% NaOCl; in low concentration to prevent the negative effect of the survival of stem cells in the apical pulp, and thus achieve the ideal conditioning of the dentin in regenerative endodontics [23]. In a study evaluating these two irrigants, it was shown that in NaOCl-treated dentin, resorption lacunae were found at the cell-dentin interface created by multinucleated cells with clastic activity. After EDTA use, dental pulp stem cells adjacent to the dentin formed an intimate association with the surface, differentiated into odontoblast-like cells expressing dentin sialoprotein and prolonged cellular processes towards the dentin tubules and a vascularized soft connective tissue similar to dental pulp was observed inside the dentin cylinder [24]. Therefore, this type of irrigation has also been shown to be effective for further bacterial reduction as in immature teeth necrotic by irrigation solutions [25].

3.2.3 Manual mechanical debridement

Another step in regeneration is to perform mechanical debridement as part of the therapy to debride the biofilm on the canal walls and eliminate bacteria in the dentinal tubules [26]. A critical component of the regenerative endodontic process is the use of a scaffold for the apical papilla stem cells to attach, multiply and differentiate [47], a cross-linked collagen scaffold is recommended and exposure of the dentin matrix combined with a blood clot may provide an effective approach to generate a life-supporting structure [28].
The disinfection process should be carried out with greater caution, as this is a part with a wide exit into the periradicular tissues could cause an operative accident. Sodium hypochlorite is the disinfectant of choice.

3.3 Current methods in pulp regeneration

3.3.1 Use of stem cells in pulp regeneration

Nowadays, a change and advance in cell biology and tissue engineering techniques can be seen, and the use of biological therapy to regenerate dental pulp has become a new trend [29]. There are new methods for stem cell-based regenerative therapy as a promising therapeutic approach for a variety of diseases [30], as well as for the preservation of vital dental pulp and nerve components. Due to the immense potential for neurovascularization, mesenchymal stem cell transplantation has shown promise [31] in terms of *in vivo* pulp-dentin regeneration by autologous transplantation [7]. However cell homing strategies for pulp regeneration need further understanding and improvement if they are to become a reliable and effective approach in endodontics [32]. Human exfoliated deciduous tooth stem cells have been studied and have been found to be a promising tool due to their ability to secrete multiple factors that are essential for tissue

regeneration, which is achieved by minimally invasive procedures compared to other treatments [33].

3.3.2 Triple antibiotic paste

One of the most widely used tools is the triple antibiotic paste composed of metronidazole, ciprofloxacin and minocycline, which exhibits promising and long-lasting antibacterial effects at appropriate concentrations, with low cytotoxicity, and effectively promotes the preservation and regeneration of pulp tissues and the formation of dental hard tissues. However, there are also problems such as tooth discoloration with one of the drugs and bacterial resistance to one of them [34].

3.3.3 Antibiotic nanofibers

On the other hand, it has been observed that three-dimensional antibiotic-eluting nanofibers combined with injectable scaffolds, enriched or not with stem cells and/or growth factors, can increase the probability of achieving dental pulp regeneration [35]. In a study evaluating lncRNA HRL-SC (hypoxia-responsive long non-coding RNA in stem cells) promotes proliferation and migration of human dental pulp stem cells through the PI3K/AKT signaling pathway, and this understanding may facilitate the regenerative application of human dental pulp stem cells [36].

The use of stem cells has obtained excellent results due to their potential to restore pulp neurovascularization, in addition to being a less invasive treatment. This is followed by the use of triple antibiotic paste, which has been a more common method and has been used for a long time.

3.4 Limitations and future of regenerative endodontic therapy

3.4.1 Regeneration of dentinopulpal structures

The main focus within tissue regeneration has been seen as a very attractive alternative therapy because it can regenerate structures and functions of the dentin-pulp complex [37]. The expected future results of the treatment, the most important are pulp revascularization with accelerated dentin formation leading to pulp canal obliteration, cementum and periodontal ligament ingrowth, cementum and bone ingrowth [38]. Based on various reports that have been made, it is mentioned that regenerative endodontic procedures have the potential to be used to treat traumatized teeth with horizontal root fracture and inflammatory root resorption [39], it has been observed that the tissues formed in the revitalized tooth canal are similar to cementitious tissue or similar to bone and fibrous connective tissue [40], the continued root development of revascularized immature permanent necrotic teeth depends on whether Hertwig's epithelial root sheath survives in case of periodontitis/apical abscess.

3.4.2 Future complications after pulp regeneration

Regarding complications of revascularization, severe calcification of the pulp canal due to hard tissue formation and ankylosis have been studied [41]; as well as esthetic problems with tooth color should be considered when using minocycline as a canal medication [42] and it has been proven that using materials such as Endo Sequence and Biodentine (taking into account that this has the lowest discoloration potential among the materials tested [43]) had significantly less discoloration [44]. In a study that evaluated the treated teeth after four months, radiographic examination of the teeth showed signs of root development after treatment, histological examination of the tissues growing in the root canal space of these teeth showed the presence of connective tissue, bone and cementum formation, and thickening of the roots [45]. So it can be said that pulp-like tissue can be regenerated de novo in the empty root canal space using stem cells from the apical papilla and dental pulp stem cells that give rise to odontoblast-like cells that produce dentin-like tissue in the existing dentin walls [46].

After regenerative treatment, root development is expected to be complete and in the best case the pulp will regain its sensitivity, although undesirable changes such as canal obliteration or ankylosis of the tooth may occur.

4. Conclusions

Endodontic regeneration therapy is a great tool within the specialty of endodontics as it has been shown to give excellent results, sodium hypochlorite has been the best method for disinfection within the treatment as manual scaling has been a risky tool because it can damage the tooth, The use of stem cells has been seen to be an excellent tool for the aid of pulp regeneration, what is expected from the regeneration is the completion of root development and regeneration of pulp tissue although a risk that may arise is an obliteration of the canal or ankylosis.

5. Conflict of Interest

Not available

6. Financial Support

Not available

7. References

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