Chapter

Regenerative Endodontic Procedure in Immature Permanent Teeth

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Abstract

This literature review will aim to recapitulate the different factors involved in the endodontic regenerative procedure, with a focus on different bacterial disinfecting techniques, intra-canal dressings and expected treatment outcomes. The electronic databases searched were EMBASE, MEDLINE and PUBMED. Articles included were limited to the English language from the year 1988 to May 2019. A hand search of the literature was also performed for articles dating back to 1958. No clear guidelines were available regarding follow-up and expected treatment outcomes in terms of success, survival (acceptable) or treatment failure. However, calcium hydroxide as an intra-canal medicament was found to be the best treatment modality in comparison to antibiotic paste for intra-canal dressing.

Keywords: regeneration, endodontics, dentistry, necrotic pulp

1. Introduction

It is widely recognised that full maturation of the root apex of permanent tooth is expected to occur three years after the time of eruption. During this period, an immature tooth may encounter situations such as traumatic injury, extensive caries and dental anomalies to the developing dentition, which in turn may lead to pulpal necrosis. This will hinder root maturation and will cause premature loss of the permanent dentition.

Necrotic immature teeth exhibit challenges for cleaning and shaping due to the presence of wide pulp canals, thin fragile walls and blunt root apices. In addition, it is difficult to obturate such a wide canals with large open apices to obtain hermetic apical seals.

At first, necrotic immature teeth were treated by calcium hydroxide apexification [1], which requires multiple visits to a clinic in order to change the calcium hydroxide dressing until a hard apical barrier is formed. However, long-term calcium hydroxide dressings will negatively affect the root canal dentine flexural strength and will make the tooth more susceptible to fracture [2, 4]. The apexification procedure was later modified by introducing an artificial hard barrier, Mineral Trioxide Aggregate (MTA) [3]. MTA apexification can be done in one or two sessions and provides a more reliable apical bacteria-tight seal. It also is biocompatible with periapical tissues and promotes hard tissue barrier formation [4]. However, MTA apexification does not induce root maturogensis, leaving the immature tooth

with thin root walls that are susceptible to fracture. On the contrary, regenerative endodontic procedures can help stimulate the formation of a new pulp/dentin complex in the pulp canal space, which will put the tooth in a more favourable physiological status [5].

Regenerative endodontic procedure (REP) is a biologically based treatment that aims to heal periapical periodontitis and substitutes the damaged structure including dentin, cementum, and cells of pulp/dentin complex in order to continue the tooth-growing process. Although the histological characteristics of dentin/pulp tissues are not yet clear, radiographic evaluation has revealed a resolution of periapical lesions, an increase in root length to complete apical root formation, and a thickening of canal walls.

The idea of revitalization of lost tissues in the empty root canal was discussed first by Nyggard Ostby in 1961 [5]. He suggested that introducing a blood clot into the sterilized pulp canal would stimulate new tissue formation and heal the periapical pathosis. His hypothesis was based on the significance of blood clots in the healing of fractured bones [6].

In the histologic analysis, Ostby [5] noted connective tissue ingrowth inside the pulp canal, with scattered islands of mineralized tissue implanted into the newly formed connective tissue. In addition, the signs and symptoms of the necrotic teeth had disappeared and the apical radiolucency had healed. Although no odontoblasts were observed in the histological analysis and unwanted cells (cementoblast) were present, the presence of fibroblast and newly formed tissues was the foundation for regenerative endodontic treatment.

In 1971, Ostby and Hjortdal [7], published a case series of regenerative treatments, but they used antibiotics in the disinfection protocol. They observed an increase in root length, healing of periapical lesions, and a resolution of signs and symptoms.

The contemporary REP was first published in 2001 by Iwaya et al. [8] In this case, the author reported on a necrotic immature premolar treated with sodium hypochlorite (NaOCl) and hydrogen peroxide (H_2O_2), then dressed with a double-antibiotic paste (DAP), which consist of metronidazole and ciprofloxacin **Figure 1**. This treatment protocol resulted in the resolution of inflammatory signs and symptoms, full root maturation and response to cold test. The second case by Banchs and Trope in 2004 [9] used NaOCl and chlorohexidine (CHX) to disinfect the canal

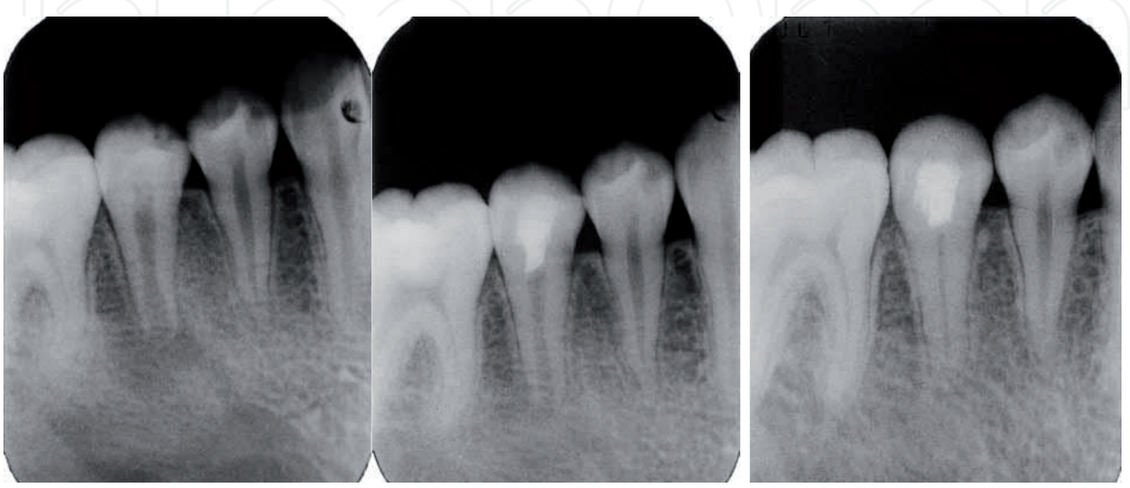

Figure 1.
On the left side, pre-operative radiograph of lower right 2nd premolar with open apex, incomplete root formation and periapical radiolucency. In the middle, radiograph taken after five months of calcium hydroxide dressing. On the right side, 35 months after treatment completion revealing complete root formation increase in root width and length [8].

chemically and employed a Triple Antibiotic Paste (TAP) containing metronidazole, ciprofloxacin, and minocycline, and observed the same result of Iwaya et al. [8].

These two cases established the fundamentals for the recent regenerative case reports. The fundamentals were the removal of bacteria and disinfecting the root canal; establishment of a scaffold; the introduction the stem cells for new tissue formation; and having a coronal bacterial tight seal to prevent recontamination of the root canal system.

Several terms had been used in case reports to describe the ingrowth of new tissue inside the root canal. These are revascularization, revitalization and regeneration. Revascularization is defined as the re-establishment of vascular supply to the already-present pulp of the immature tooth [10]. Revitalization is defined as the ingrowth of tissue that may differ from the initial original tissue [11]. Endodontic regeneration is defined as the replacement of lost or damaged structures including dentine, root structures and cells from pulp/dentin complex, by another structure [12].

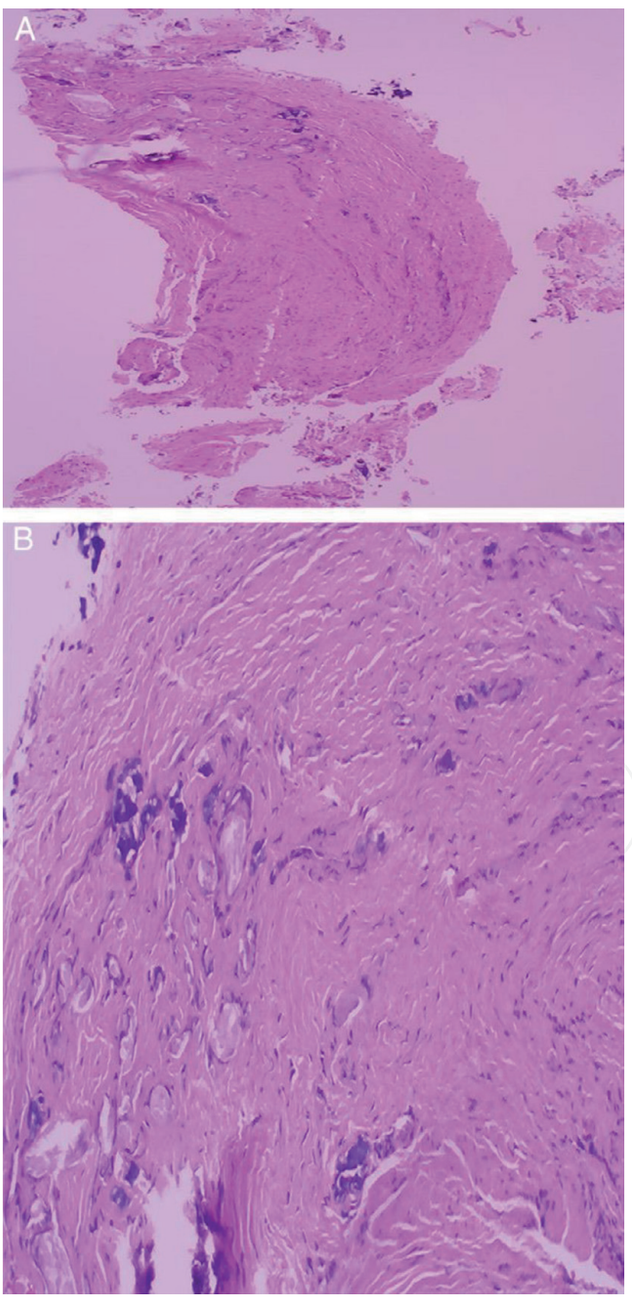

Figure 2.
(A) Pulp like connective tissue generated in human tooth after Regenerative Endodontic Therapy. (B) Higher magnification of the soft tissue showing the presence of collagen fibers, cells, and blood vessels in this tissue [13].

Lately, there have been two histological case reports of teeth extracted after having endodontic regenerative treatment. [13, 14] These studies gave a clearer idea of what was happening inside the canal after regeneration.

In the first histological case report [13], the tooth became painful and symptomatic 14 months after receiving regenerative treatment. When the pulp was extirpated and examined histologically, the author found a vital loose pulp-like connective tissue **Figure 2**.

In the second histological report [14], three and a half weeks after regenerative treatment was completed, the tooth had a complicated crown root fracture that left the remaining tooth structure beyond restoration. After extracting the tooth, the pulp canal content was examined histologically; the author reported the content of the pulp canal as a loose connective tissue, similar to pulp tissue, but histologically proven to be not pulpal tissue.

The histological findings of these two case reports did not provide sufficient evidence to represent all teeth that had undergone an endodontic regenerative procedure. However, the available findings suggest that tissue regeneration is occurring inside the root canal. Accordingly, endodontic regenerative procedure is the most relevant term to describe the type of tissue grows in the pulp canal.

2. Case selection

The regenerative endodontic procedure is a biologically based procedure in which good case selection will have an impact on the outcomes. The recent recommendations of the American Association of Endodontists (AAE) suggest that the regenerative endodontic procedure should be carried out in teeth with necrotic pulp and immature roots, and that the root canal space should not be utilized to retain a coronal restoration in the future. In other words, the selected tooth should have enough coronal tooth structure that it will need a post to retain the coronal core [15].

It would appear that the aetiology of pulp necrosis does not play a role in case selection here; many regenerative endodontic case studies did include necrotic immature teeth with different aetiologies, whether the pulp necrosis was caused by a caries lesion [16], was secondary to trauma [17] or due to dental anomalies [9].

In view of the fact that root canal space will be occupied by a blood clot and a bacterially tight hard barrier, teeth with insufficient remaining tooth structure are not recommended to be selected, since this would require further retentive means (post). In addition, in some cases, if the tooth structure loss is massive, isolation might become problematic. Patient and/or parental cooperation is necessary, as the treatment requires multiple visits and regular monitoring and follow-up appointments. Furthermore, the consent form must be signed.

The chances of success for teeth with immature root apices to be re-vascularized are significantly higher than for teeth with fully or nearly fully formed root apices. This could be attributed to the better ingrowth of vasculatures and stem cells flow in the pulp canal.

A study by Kling et al. [18] on re-implanted teeth noticed that teeth with apical foramen diameters of 1 mm or less had no chance of re-vascularization. In different circumstances, teeth with apical foramen diameters ranging from (1.1 mm - 5.0 mm) had spontaneously vascularized 18% of the time. They noticed also that when extra-oral time was under 45 minutes re-vascularization significantly increased; 39% of the teeth re-vascularized with shorter periods, compared to 11% only with longer periods ($P < 0.05$).

In addition, blood samples taken from incomplete root apices showed levels of CD 73 and CD 105 (Mesenchymal stem cell markers) almost 600 times higher than in samples obtained from the circulating blood stream, indicating the higher availability of stem cells in the apical dental papilla of immature roots [19].

Lovelace et al. did not obtain samples from mature roots for comparison. This could have produced similar results. However, the findings are supported by another study that apical papilla of the immature root apices represent a superior reliable source of stem cells that possess high surviving and cells turn over levels [20].

Immature roots with periapical pathosis of endodontic origin can undergo the regenerative endodontic procedure. Many published case reports have revealed potential root maturation in non-vital immature permanent teeth with the presence of periapical lesion or apical abscess [8, 9, 21, 22] that produced a complete resolution of the apical radiolucency in addition to a successful root maturation.

There are three possible explanations for this. The first is that immature roots with open apices allow easy communication between the root canal pulp and the periapical area. This may allow infection and inflammatory cells to reach the apex quickly while the pulp tissue is partially vital. In addition, the stem cells in the pulp and periapical papilla could survive the infection due to the high vascularity. Thus, the stem cells still can differentiate and allow root maturation in spite of the ongoing infection. The second explanation is that in young patients, the majority of the jawbone is cancellous and the bony trabeculations are larger. Therefore, resorption and periapical radiolucency may be formed in a short period and not all of the pulp tissues had turned necrotic [20]. Finally, the periapical radiolucency could be related to the apical dental papilla, where a radiolucent shadow of the dental papilla is expected and not necessarily to periapical pathology.

As a general statement, regenerative endodontic procedures should be performed if the patient is not allergic to any of the antibiotics or the medicament or irrigation agents that are usually used in sterilizing and dressing the canal in this procedure. In addition, patients should be classified as American Society of Anaesthesiologist (ASA) I or ASA II physical status. ASA I means that the patient is healthy and is a non-smoker, with no or minimal alcohol consumption. ASA II defined as with a mild disturbance without any significant functional limitations, for example if a person is fit and well but a smoker or social alcohol consumer. In addition, pregnancy, controlled Diabetes mellitus, and obesity (BMI over 30 and less than 40) all fall into ASA II classification.

This requirement is to ensure better tissue healing and a favourable response toward a stem cells differentiation, and thus continuation of root maturation without complication.

3. Endodontic regeneration in an infected root canal

Given the proper environment, many body tissues are programmed to regenerate new cells in order to compensate for lost ones; dental pulp tissue is no an exception. One of the most critical factors for regeneration is a bacteria-free root canal to allow stem cells to continue to regenerate and grow the root further into its full maturation without any damage.

Sterilizing an infected root canal can be sometimes quite challenging since roughly 20 different bacterial species can be found in an infected root canal with chronic apical periodontitis [23]. In addition, the root canal anatomy can provide a good sanctuary for the microbiota to thrive, containing places antimicrobial agents have difficulty reaching, for example accessory canals, isthmuses and fins.

Teeth can be subjected to many conditions in which lead to bacterial contamination of the root canal. The most prevalent are caries lesions, traumatic injuries and dental anomalies. Caries lesions can cause pulp exposure in teeth with immature apex, often in the permanent first molars. Permanent first molars erupt at an early age (6 to 7 years old), often when children are not sufficiently skilled in maintaining adequate oral hygiene on their own. This explains why caries is more prevalent in children who live in families of low socioeconomic status that have the inadequate oral hygiene and/or poor dietary habits that lead to early dental caries [24].

3.1 Sequelae of pulpal infection in immature root canal

Caries exposure related to vital pulp can present clinically with mild to moderate symptoms. In this case, vital pulp therapy like pulp capping [25] or pulpotomy [26, 27] using calcium hydroxide [$Ca(OH)_2$] or Mineral Trioxide Aggregate (MTA) would allow full root maturation. In spite of this treatment approach, usually the pulp goes necrotic and presents with asymptomatic or symptomatic apical periodontitis.

Periapical radiolucency of the dental follicle in immature teeth makes it hard to diagnose periapical periodontitis from dental radiographs. For this reason, apical periodontitis should be confirmed with clinical examinations such as cold tests, percussion, palpation, swelling and the presence of sinus tract. Once the pulp is confirmed to be necrotic in an immature tooth, a regenerative procedure may allow normal root maturation.

3.2 Dental anomalies that contribute to pathogenesis of pulp in immature teeth

Among congenital tooth anomalies, dens evaginatus is the most prevalent anomaly that causes early pulp devitalization and subsequent pulp necrosis in immature teeth [9, 28]. Dens evaginatus is a developmental anomaly causes a formation of accessory cusp (tubercle) project in the tooth surface. This tubercle consists of enamel, dentin and pulp tissues. With normal physiological tooth wear, the pulp gets exposed, leading to asymptomatic pulp necrosis in immature teeth [29]. Nevertheless, pulp exposure can be avoided if the tubercle is discovered early. Simple occlusal adjustment and topical fluoride application increases the enamel hydroxyapatite which contributes to enamel remineralization. Another treatment option would be the use of flowable composite resin sealant or in the case of pinpoint pulp exposure shallow pulpotomy using layer of tri calcium silicate cement (MTA, Biodentine®) or calcium hydroxide would be a conservative solution in case of dens evaginatus and thus avoid early pulp devitalization. Dens invaginatus is described as the folding of enamel into dentine which increases the risk of caries development and pulpal involvement. However, pulpal exposure can be avoided by simple preventive measures such as a fissure sealant.

4. Endodontic regeneration in traumatized teeth

Many studies have revealed some situations in which an immature root may regenerate pulpal tissue and dentine after trauma spontaneously. Kling et al. [30] monitored 154 replanted avulsed teeth (72 were immature teeth) radiographically for pulp revascularization.

In all mature teeth with apical foramen width 1 mm and smaller, revascularization did not occur, while 18% of the immature teeth (apical foramen width larger than 1.1 mm) revealed signs of revascularization. Instead, all teeth that did

not respond to pulp revascularization revealed signs of periapical lesions and/or external resorption. Post-operative systemic antibiotics did not have any effect on the probability of pulp/dentine revascularization in replanted avulsed teeth in this study. The same result regarding post-operative systemic antibiotic use after avulsed teeth replantation was found in a later study by Andereason et al. [31] Two types of hard tissue formation were found in teeth with revascularized pulp. There was either normal root maturation in both length and thickness of the root, or radiopaque material separated from the root and continued to grow with alveolar bone, while the tooth length arrested. [32].

4.1 Effect of extra oral time of avulsed tooth on spontaneous regeneration

Extra-alveolar time can be defined as the time that the avulsed tooth spends out of its original socket. Andersson et al. [32] Found that extra-alveolar time of avulsed teeth was less than 45 minutes, the probability of revascularization was 39%, compared to 11% in teeth with extra-alveolar time more than 45 minutes. 60 minutes of extra-alveolar time can cause necrosis of the Periodontal Ligament (PDL) membrane and cells, which leads to external root resorption and the inhibition of further root development. When avulsed teeth are implanted immediately or within 15 minutes, no resorption was noted. In addition to this, after 15 minutes, replanted avulsed teeth revealed some root resorption but not in a progressive pattern [32]. Extra-alveolar time of less than 45 minutes shows better root formation and less inflammatory resorption when compared to times longer than 45 minutes. There was no significant difference in regeneration and subsequent root formation between different extra-alveolar storage media (dry medium, wet media [saliva, tab water, etc.], and combination medium [dry then wet]) for the avulsed tooth. Although it is not significant, a dry extra-alveolar time of less than 45 minutes led to more frequent root formation and completion [33].

For avulsed teeth kept in a wet storage media (saliva, tap water, etc.), the survival of the pulp is significantly greater when it is kept for less than 5 minutes. This is because only part of the pulp that communicates with the storage medium is the pulpal tissue in the apical foramen; the body of the root protects the rest of the pulp. However, if the apical foramen were to be contaminated with bacteria due a longer duration of storage, the vascularization process as a whole would be jeopardised [31].

The extent of root maturation is related to the pulp revascularization; in healing pulp, more root maturation is found compared to necrotic pulp. Immature roots with large apical foramen had more tendencies toward pulpal tissue regeneration; large apical foramen facilitates the flow of apical papilla stem cells into root canal easier than a mature, narrow apical foramen.

4.2 Factors that could contribute to REP in traumatized teeth

A factor that had a strong correlation with pulp regeneration in avulsed teeth is the length of the pulp canal (the distance between the apical foramen and pulp chamber). Since pulp regeneration may be arrested by infection process, the longer the distance to be regenerated, the more chances there are of an infection occurring, and thus less chance for the pulp to regenerate [34]. The correlation between the length of the pulp canal and the probabilities of pulp revascularization has also been found in another study of revascularization of auto-transplanted 370 premolars [35].

Partial or arrested root formation is generally followed by bone ingrowth and formation of internal PDL tissues. Hertwig's epithelial root sheath (HERS) is

presumed to prevent the invasion of bone and PDL derived cells inside the canal and thus reduce disturbance to root development. This presumption is explained by a partial or total loss of HERS being accompanied by partial or arrested root development. In case of pulpal necrosis, root development and maturation may occur because HERS can tolerate trauma to avulsed tooth and damage by extra-alveolar time [33].

The predominant root resorption found in replanted avulsed teeth is external replacement resorption (Ankylosis), followed by inflammatory root resorption and finally, external inflammatory surface resorption. Inflammatory root resorption is most common in immature roots, while replacement resorption (ankyloses) is found more in mature roots [36]. Although bone remodelling is higher in young adolescents, rate of resorption in general is not affected by age. However, if the HERS and PDL are viable, age would not make a difference in the rate of resorption. In addition, Root Canal Treatment within the first three weeks (usually the third week) after tooth replantation can reduce the rate of resorption [32].

5. Follow up

In follow-up visits, clinical and radiographic outcomes should be evaluated. Clinical evaluation includes absence of pain on percussion and palpation, no presence of soft tissue swelling and disappearing of sinus tract if present before treatment. The tooth response to sensibility tests (cold and EPT) should be recorded, but the absence of response does not indicate treatment failure. Radiographic evaluation includes: resolution of pre-treatment periapical radiolucency if it was present, further root length maturation and an increase in canal wall thickness.

There is no standard follow-up protocol after endodontic regenerative procedures as of yet. Nevertheless, in the published endodontic regenerative case reports, the follow-up ranged from 6 months [37] up to 60 months [38] after completing treatment. The European Society of Endodontology recommends follow-up and recall appointments every 3, 6, 12, 18 and 24 months, with annual recall after the follow-up period for the next 5 years [39].

In most endodontic regenerative cases, enhancement or resolution of periapical lesion is expected in the first 6 months. Wiggler et al. [40] endorse a recall every three months in the first year after completion of treatment and then every six months, unless symptoms developed.

6. Conclusions

In conclusion, regenerative endodontic procedure is a non-invasive treatment that restores the dentin/pulp complex in necrotic immature teeth, and is now an essential part of the endodontic speciality. In many case reports it shows a promising potential for saving necrotic immature teeth and helping the continuation of root maturation. Unlike conventional MTA or calcium hydroxide apexification, it tends to promote further root development and increases root canal wall thickness, which will improve the overall survival of the tooth.

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