Regenerative Endodontics: A Potential Solution for External Root Resorption (Case Series)

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SIGNIFICANCE

There is no definitive treatment for arresting replacement root resorption. This case series shows the potential of regenerative endodontic treatment using PRF to arrest inflammatory root resorption as well as replacement root resorption.

ABSTRACT

Introduction: Regenerative endodontic procedures (REPs) are aimed to treat apical periodontitis and promote root maturation of immature necrotic teeth. However, REPs are not intended to be a primary indication for treating or arresting external root resorption (ERR). The purpose of this study was to describe REP treatment in the cessation of ERR. **Methods:** Four cases (5 teeth) of posttraumatic immature teeth diagnosed with necrotic pulp and apical periodontitis or chronic apical abscess were treated with REPs using plasma-rich fibrin as a scaffold. All the teeth showed ERR and have been followed up to 3 years. **Results:** This case series shows how REPs arrested ERR. In 3 of the cases, replacement resorption was arrested, thus avoiding complications of ankylosis and the need for decoronation. **Conclusions:** In addition to the known advantages of REPs, we show that REPs are a promising treatment modality for arresting ERR, warranting further clinical trials. *(J Endod 2020;46:192–199.)*

KEY WORDS

Ankylosis; dental trauma; external inflammatory root resorption; platelet-rich fibrin; replacement resorption; regenerative endodontic procedure

External root resorption (ERR) often is a consequence of severe trauma. External inflammatory root resorption (EIRR) is 1 type of ERR. EIRR is a pathologic process that occurs after a range of mechanical or chemical stimuli such as infection, pressure, trauma, or orthodontic tooth movement leading to inflammation and loss of the root protective barrier[1]. Replacement resorption (RR), a second type of ERR, is manifested by various stimuli that induce inflammation as well as the loss of viable periodontal ligament cells. EIRR and RR after dental trauma are high-risk complications often observed in children[2]. Until recently, treatments aimed at arresting EIRR were unpredictable and often ineffective[3–5]. Calcium hydroxide intracanal dressings, the preferred treatment for EIRR, attenuate the progression but do not arrest resorption. Similarly, the management of RR after evidence of ankylosis usually includes decoronation and root submergence. However, both treatment modalities are less than ideal for tooth retention. Recently, Tzanetaki[6] described a case in which a regenerative endodontic procedure (REP) with a blood clot as the scaffold showed arrested EIRR of tooth #9, which underwent trauma-induced intrusion. Along the 30-month follow-up period, progressive healing and remodeling of the lamina dura were detected. Although this showed an additional benefit of REPs, some limitations to performing REPs with a blood clot remain.

REPs are known to rely on 2 factors: disinfection and stem cell–mediated processes that promote root development. Evoked bleeding has traditionally been the method of choice for ingress of stem cells from periapical tissues. However, bleeding is not a predictable clinical outcome[7]. Moreover, laceration of the periapical tissues can potentially damage cells needed for epithelial-mesenchymal interactions. Furthermore, a fibrin blood clot is unstable and prone to breakdown[8]. Therefore, other autologous scaffolds depending on a combination of thorough chemical disinfection with 3 additional factors (stem cells, growth factors, and a scaffold) were developed to promote cellular growth and differentiation of the stem cells[9]. Blood concentrates (eg, platelet-rich plasma [PRP] and platelet-rich fibrin [PRF]) have been shown to be superior substitutes because they contain more stem cells and growth factors and can predictably be introduced in the canal system, thereby overcoming the shortcomings of a blood clot[7,10]. To this end, Choukroun et al[11] developed the protocols and applications of PRF, which is considered a second-generation platelet concentrate. It is an autologous platelet and leukocyte mesh that serves as a reservoir for slow, continuous release of growth factors over a period of 7 to 14 days, unlike PRP whose effect is limited to the first 24 hours. PRF incorporates leukocytes, platelets, and a wide range of key

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healing proteins in a dense fibrin matrix. Furthermore, PRF acts as a chemoattractant for neighboring stem cell populations, leading to the induction of regeneration and mineralization[12]. Therefore, the aim of this study was to describe clinical outcomes of PRF use in arresting trauma-induced ERR.

MATERIALS AND METHODS

Common Clinical Procedures

Four patients (5 teeth) who developed external resorption (inflammatory or replacement resorption) were treated by a single REP after their guardians signed an informed consent form. Table 1 describes the age, sex, tooth number, diagnosis, duration of intracanal medication, and follow-up period.

Medical and dental history was obtained for all patients followed by a thorough oral and dental examination. Mobility and sensibility tests, the electric pulp test, and probing and percussion tests were performed. Two-dimensional diagnostic radiographs were taken, and the diagnosis was established in the involved teeth (Table 1).

All patients were treated at their first appointment under local anesthetics (lidocaine 2% 1:100,000 epinephrine; Safco, Buffalo Grove, IL) using a surgical operating microscope (Prima; Labomed, Los Angeles, CA). After tooth isolation and access opening, all cases were treated with an REP according to the American Association of Endodontists' protocol[13]. Each tooth was irrigated with 20 mL 1.5% hypochlorite; dried with paper points; and dressed with triple antibiotic paste (trimix), a mixture of equal parts (250 mg each) of 3 antibiotics: metronidazole (Sanofi-aventis, Paris, France), cefuroxime axetil (Zinnat; GSK, Brentford, UK), and ciprofloxacin (Dexcel, Or Akiva, Israel). The antibiotic tablets were crushed and then dissolved in saline to a creamy paste consistency for a period of 3 weeks. All teeth were then temporarily restored using Interim Restorative Material (Dentsply Sirona, York, PA).

At the second appointment (Table 1), after examination and assuring that the patient was asymptomatic, PRF was prepared from 40 mL blood drawn by a qualified nurse from the respective patient's cubital vein in his or her right forearm with a butterfly needle (BC12; Zhejiang Kindly Medical Devices Co, Longwan, China) for all of the patients. The blood sample was centrifuged for 8 minutes at 1300 rpm (11). Patients were then anesthetized using mepivacaine 3% (Septodont, Saint-Maur-des-Fossés, France). Under rubber dam isolation, the temporary restorative material was removed, and the root canal was irrigated with 20 mL 17% EDTA[14]. After drying the root canal with paper points, prepared PRF was inserted using endodontic pluggers up to the level of the cementoenamel junction. A Resorbable Collagen Plug (Collagen Matrix, Inc, Oakland, NJ) was inserted above the PRF and covered with Biodentine (Septodont), a bioceramic material. The coronal part was sealed with glass ionomer (Fugi IX; GC Corp, Tokyo, Japan). During the first year, 3-month follow-up appointments were scheduled for each patient.

RESULTS

Case Report 1

A 12-year-old boy was referred to an endodontic specialty practice by a general dentist after root resorption was diagnosed in teeth #8 and #9. The boy's parent reported a history of dental trauma but could not remember what had occurred and when. The medical history was unremarkable. Clinical examination revealed normal soft tissues and that teeth #8 and #9 were negative to cold and palpation. All probing depths were <3 mm. Percussion testing revealed tenderness on teeth #8 and #9, which also produced a metallic sound indicative of ankylosis. Radiographic examination showed a closed apex in both teeth and the beginning of resorption on tooth #8 in the distal midroot and mesial cervical area. Advanced resorption of the distal side of the root was also observed in tooth #9 as well as a periradicular lesion coronal to the apex (Fig. 1*A*). A diagnosis of necrotic pulp with symptomatic apical periodontitis was made, and REP was elected as the treatment of choice for both teeth. Clinical procedures for REP were performed (Fig. 1*B*) as described previously. At the 3-month follow-up appointment, both teeth were asymptomatic and tested negatively in all clinical tests. Radiographs showed no further progression of resorption and healing of the periradicular area (Fig. 1*C*). Slight apical closure was visible in tooth #9. No changes in root width or length were noted. At the 30-month follow-up examination, both teeth continued to be asymptomatic and revealed a negative response to thermal testing with percussion and palpation responses within normal limits. Percussion testing did not reveal any metallic sound in either tooth that was noted preoperatively. Radiographs taken on the same visit revealed no changes in tooth #8 and the development of a calcified bridge 3 mm coronal to the apex. Resorption appeared to be arrested in both teeth. Additionally, a radiograph of tooth #9 showed significant apical closure compared with the 3-month follow-up radiograph (Fig. 1*D*). A normal periodontal ligament surrounded the mesial and apical aspects of the root.

Case Report 2

An 11.5-year-old boy was referred to an endodontic specialty practice by a general dentist. The medical history was unremarkable. The parent reported the boy underwent avulsion of tooth #8 after a traumatic accident 3 years prior. The parent was unable to provide information on any prior treatment rendered for tooth #8. Clinical examination revealed normal soft tissues. A class III fracture (Andreasen classification) and a heavy gray discoloration were noticed in

TABLE 1 - Patients' Details

Patient age	Sex	Tooth #	Diagnosis	Ankylotic sound	Intracanal medication	Duration of intracanal medication (wk)	Last follow-up (mo)	Ankylotic sound after REP
12.0	M	8 and 9	PN/SAP	+	Trimix	3	30	–
11.6	M	8	PN/SAP	+	$Ca(OH)_2$/ trimix	4/3	22	–
12.6	F	9	PN/CAA	–	$Ca(OH)_2$/ trimix	4/3	24	–
9.0	F	8	PN/IPT	+	Trimix	3	12	+

CAA, chronic apical abscess; $Ca(OH)_2$, calcium hydroxide; F, female; IPT, initiated previous treatment; M, male; PN, pulp necrosis; REP, regenerative endodontic procedure; SAP, symptomatic apical periodontitis.

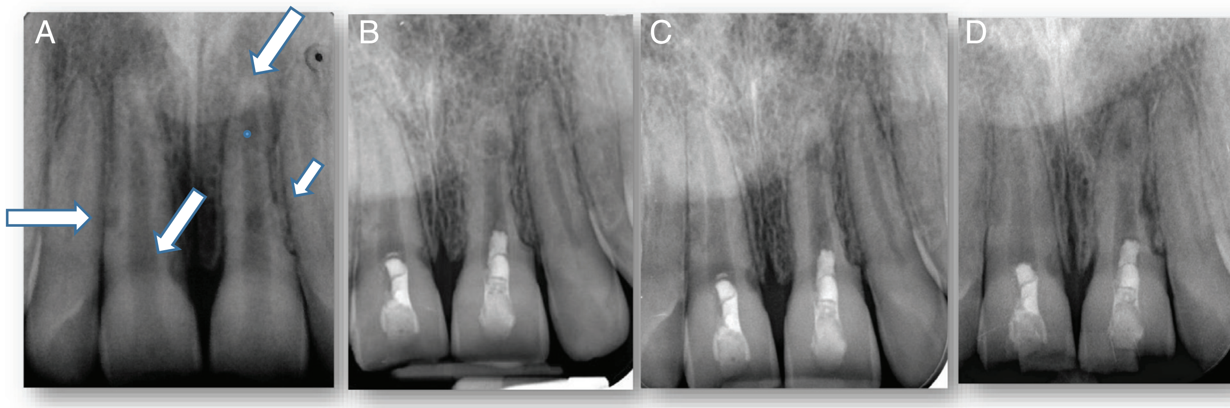

FIGURE 1 – Case 1: teeth #8 and #9. (*A*) The preoperative periapical radiograph of teeth #8 and #9 showing ERR and a periradicular lesion in tooth #9 (*arrows*). (*B*) The periapical radiograph taken upon finishing PRF insertion. (*C*) The periapical radiograph taken 3 months postoperatively showing the reduction of periradicular radiolucency size and arrest of the resorption sites. (*D*) The periapical radiograph taken 30 months postoperatively showing a slight widening of the periodontal ligament in the coronal half of the distal aspect in tooth #9.

tooth #8 (Fig. 2*A*). Clinical tests revealed tooth #8 to be negative to cold and palpation but tender to percussion with a metallic sound indicative of ankylosis. All probing depths were <3 mm. Radiographic examination revealed a wide root canal space with an open apex and substantial apical resorption with the apical third likely replaced by osseous tissue. Additionally, ERR presented on half the distal aspect of the root (Fig. 2*B*). No periapical radiolucency was noticed (Fig. 2*B*). Based on these findings, a diagnosis of necrotic pulp with symptomatic apical periodontitis was made.

At the first visit, the coronal half of the root canal was dressed with calcium hydroxide for 4 weeks, and REP was elected as the treatment of choice. Clinical procedures for REP were performed as described in the previous case (Fig. 2*C*). In a subsequent visit, the tooth was reopened, irrigated as described earlier, and the calcium hydroxide replaced by triple antibiotic paste. Two months later, the tooth was found to be asymptomatic, and a final treatment was performed (Fig. 2*C*). At the 6-month follow-up appointment, the tooth was asymptomatic and tested negatively in all clinical tests. The periodontal ligament was traceable around the entire root, except around the apex. Resorption had been arrested, and the root canal space appeared to have radio-opacities consistent with calcified tissue (Fig. 2*D*). Percussion testing did not reveal any metallic sound that was noted preoperatively. At the 22-month follow-up, the tooth continued to be asymptomatic, revealed a negative response to thermal testing with percussion, and palpation responses were within normal limits. Radiographic examination revealed an intact periodontal ligament surrounding the root, further apical elongation, and an apical barrier at the end of the root

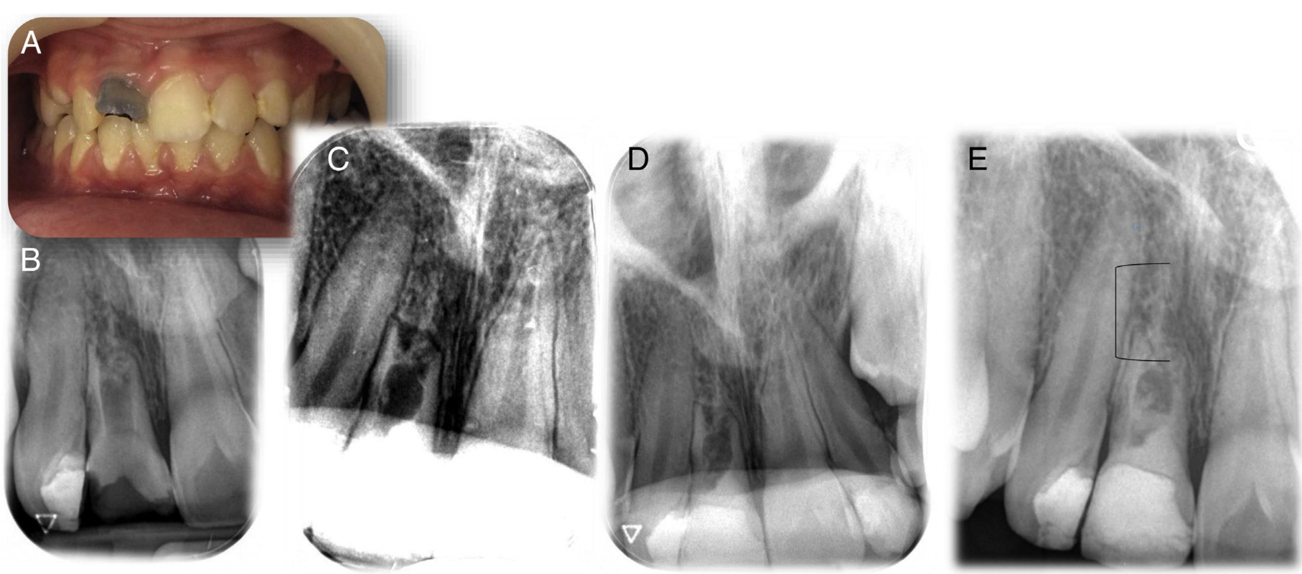

FIGURE 2 – Case 2: endodontic regenerative treatment of tooth #8 after avulsion and reimplantation. (*A*) A clinical view of tooth #8. (*B*) The preoperative periapical radiograph of tooth #8. (*C*) The periapical radiograph taken upon finishing PRF insertion. (*D*) The periapical radiography taken 6 months after the regenerative treatment. (*E*) The 22-month follow-up periapical radiograph showing root elongation (*arched arrow*).

canal. A calcified bridge had developed in the coronal part of the root canal (Fig. 2E).

Case Report 3

A 12.5-year-old girl was referred to an endodontic specialty practice by a general dentist. Her medical history was unremarkable. According to the parent, the girl underwent a traumatic accident in school 2 years prior, which caused avulsion of tooth #9. The parent remembered the tooth was kept under dry conditions for 40 minutes and then placed in milk for an additional 40 minutes. The girl was admitted to the hospital where tooth #9 was replanted and splinted for a month, after which the splint was removed with no further instructions for follow-up. Two years later, acute exacerbation with pain and swelling occurred, and the girl sought dental emergency care in a general practice. Clinical examination revealed extraoral swelling in the anterior region associated with tooth #9. Intraoral examination revealed a sinus tract was present in the buccal vestibule adjacent to the apex of tooth #9. Clinical tests revealed class 1 mobility negative to the cold test but tender to percussion and palpation. No ankylotic/metallic sound was noted. All probing depths were <3 mm. Radiographic examination revealed significant ERR and an open apex. Large periradicular radiolucency was noted, which extended to the apex of tooth #10 (Fig. 3A). A diagnosis of necrotic pulp with chronic apical abscess was made. The parents were informed about the compromised prognosis and treatments options before electing REP. Tooth #10 was found to be vital, and the treatment performed as described earlier (Fig. 3B).

At the 3-month follow-up appointment, the tooth was asymptomatic and tested negatively in all clinical tests. A remarkable decrease in periapical radiolucency was noticed on the X-ray (Fig. 3C). At the 24-month follow-up, the tooth continued to be asymptomatic and revealed a negative response to thermal testing with percussion and palpation responses within normal limits. Radiographic examination revealed arrestment of resorption and complete resolution of the radiolucent area. A calcified substance filled the root canal; in the middle third of the root canal, a calcified bridge had developed (Fig. 3D).

Case Report 4

A 9-year-old girl presented in the endodontic specialty practice after avulsion of tooth #8 three days prior. The tooth was reimplanted in a hospital after an hour of dry time and then splinted with an Erich arch (Fig. 4A). The medical history was unremarkable. Clinical examination revealed normal soft tissues. Class IV crown fractures were noted in teeth #8 and #9. Radiographic examination revealed wide root canal spaces in both teeth (Fig. 4A). A recommendation to change the Erich arch into a semirigid splint was given. The patient continued treatment in another office using prolonged dressing with calcium hydroxide. Six months later, the patient returned for further consultation because of ERR. Upon examination, tooth #7 underwent root canal treatment. Tooth #9 was vital and restored with composite filling in the next appointment. Clinical tests revealed tooth #8 was negative to cold, percussion, and palpation. Percussion testing revealed metallic sound. Periapical radiography revealed massive root resorption extending from the midroot to the apex (Fig. 4B). A diagnosis of previously initiated asymptomatic apical periodontitis was established. The parents agreed to REP after being informed about the compromised prognosis and treatments options including REP in accordance with Duggal et al[15] (Fig 4C).

At the 12-month follow-up appointment, the tooth was asymptomatic and tested negatively to all clinical tests, except the percussion test, which yielded an ankylotic sound in tooth #8. Radiographic examination revealed that inflammatory resorption was arrested followed by replacement resorption (Fig. 4D). Periradicular radiolucency seems to have healed. However, no change between the occlusion of the 2 crowns of the central incisors was observed (Fig. 4E).

DISCUSSION

The prevalence of dental injuries is approximately 18%, mostly occurring in early mixed dentition[16,17]. The most serious injuries are intrusions and avulsions[4]. Frequently, the outcome of reimplantation of avulsed and intruded teeth is root resorption. The incidence of root resorption types after avulsion and reimplantation in descending order is replacement root resorption followed by EIRR, surface root resorption, and internal root resorption[18]. The prevalence of replacement resorption because of reimplantation is approximately 61%.[19]. Trauma involving the supporting tissue presenting with sequelae resulting from neurovascular disruption, pulp necrosis, and bacterial contamination is more frequent. As complications may occur weeks, months, or even several years after injury, dental injuries require long-term follow-up[20]. Although the exact mechanisms responsible for root resorption are not fully understood, dental trauma is considered the major potential predisposing factor[21]. Soares et al[22] found in a

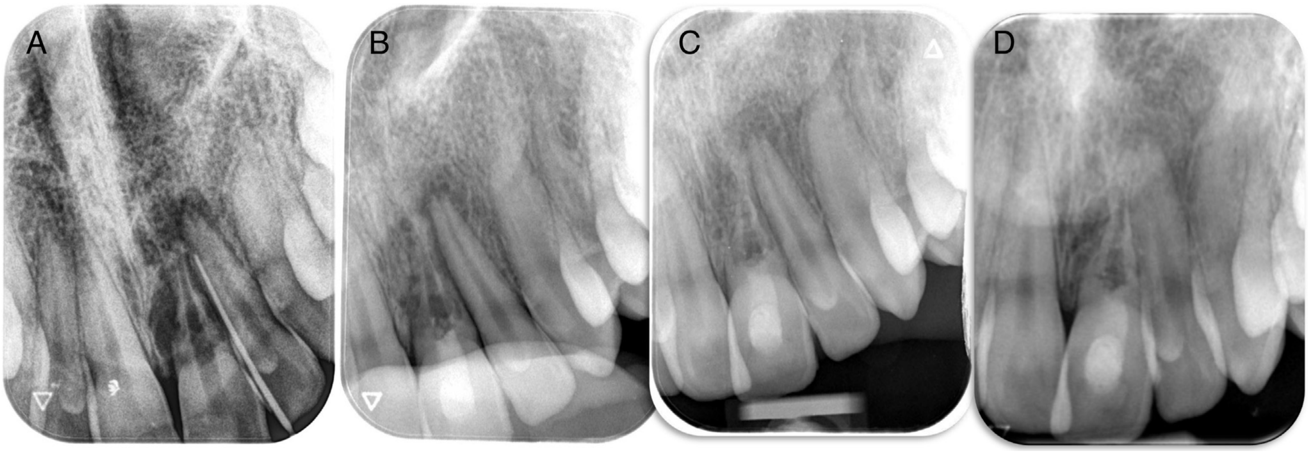

FIGURE 3 – Case 3: endodontic regenerative treatment of tooth #9 after avulsion and reimplantation. (*A*) The preoperative periapical radiograph of tooth #9. (*B*) The periapical radiograph taken upon finishing the regenerative treatment. (*C*) The 3-month follow-up periapical radiograph. (*D*) The 24-month follow-up periapical radiograph.

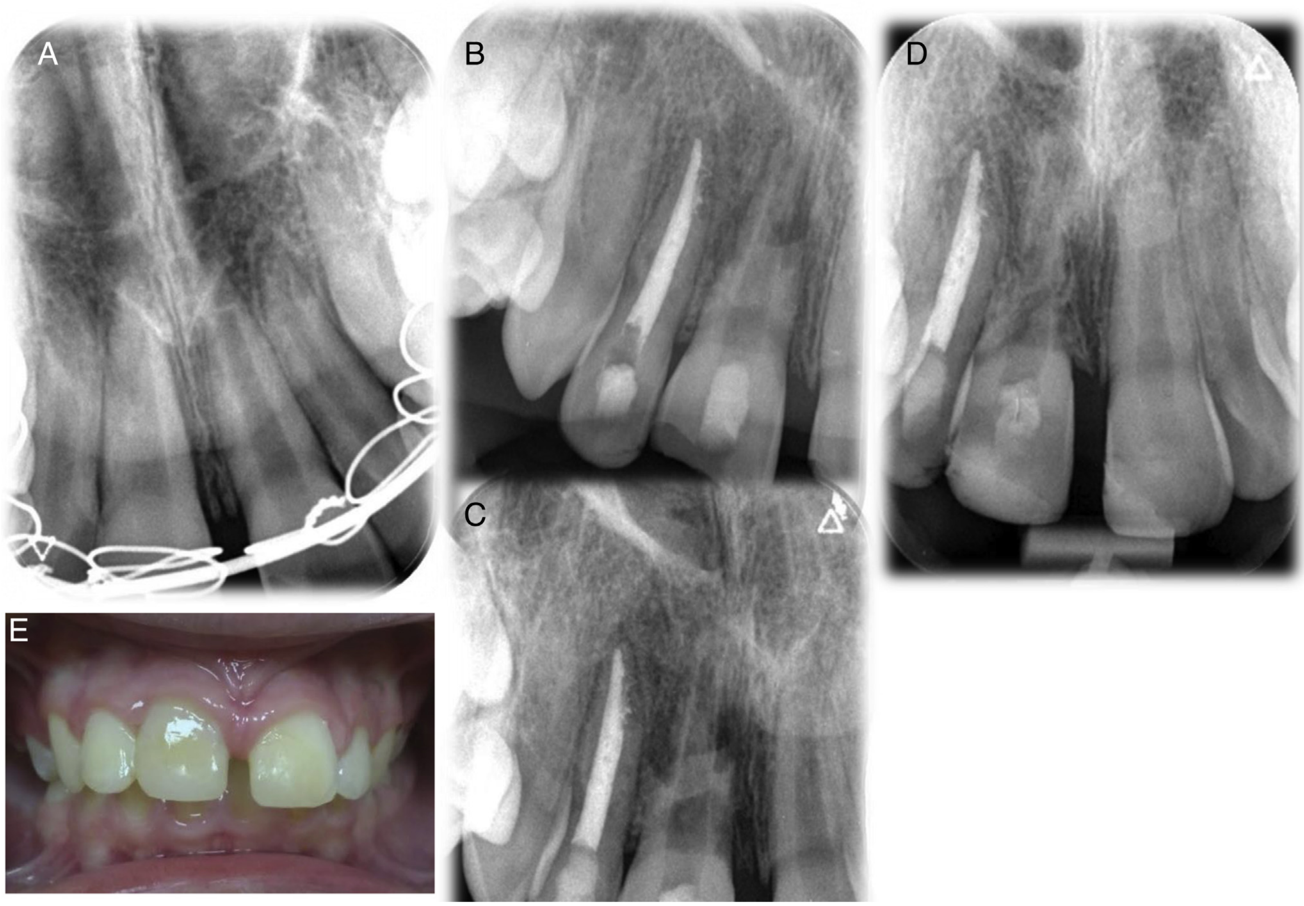

FIGURE 4 – Endodontic regenerative treatment after recent avulsion and reimplantation of tooth #8. (*A*) The periapical radiograph of tooth #8 showing the Erich arch splint. (*B*) The preoperative periapical radiograph taken 6 months after the event. Notice a massive root resorption beginning from the midroot to the apex. (*C*) The periapical radiograph taken upon finishing the PRF insertion. (*D*) The 12-month follow-up periapical radiograph. (*E*) A clinical view of the front upper teeth; there is no discrepancy in the cervical line of the crown of tooth #8 and the neighboring crowns.

retrospective study that of 249 traumatized teeth, 84.9% of the pathological resorption was represented by EIRR and was present more frequently in cases of intrusive luxation. With regard to replacement resorption, the incidence was higher in cases of avulsion. According to Campbell et al[4], the pathogenesis of ankylosis lies in the damage to the periodontal ligament cells, frequently caused by luxation injuries. Replacement resorption and, as a result of it, ankylosis are largely responsible for the low 5-year survival of teeth after such injuries[4]. Tooth loss is inevitable when ankylosis is detected in early stages. Most treatment options suggested for arresting or repair of replacement resorption are unpredictable and not supported by evidence-based clinical trials. For example, treatment with Emdogain does not cure or prevent ankylosis[23]. Therefore, there is a critical need for clinical procedures that arrest replacement resorption in a timely and predictable manner.

We hypothesize that REPs may become an alternative to arrest further advancement of replacement resorption and/or provide a means to promote new periodontal ligament attachment to ankylosed teeth. In 2001, the first case of REP was reported by Iwaya et al[24]. In 2013, the American Association of Endodontists adopted the protocol of Banchs and Trope[25] as a guideline for necrotic young immature permanent teeth. The objectives of this treatment are clinical and radiographic resolution of apical periodontitis, narrowing of the apical foramen, thickening of root canal walls, lengthening of the root, and re-establishment of pulp vitality. However, recent case reports indicate an additional and unique advantage of REPs—cessation of root resorption. The first case report describing arresting EIRR in 3 cases using REP was published in 2015 by Santiago et al[26]. In 2016, Chaniotis[27] described a single-step regenerative approach for a replanted mandibular central incisor with severe resorption. The 24-month follow-up revealed healing of the severe EIRR, continuous root development, and dentin wall thickening of the apical third, without any signs of ankylosis. In 2016, Saoud et al[28] described a series of 3 cases of traumatized teeth, all of which presented with EIRR and were treated with REPs. EIRR was resolved in all the treated teeth. In 2018, Tzanetaki[6] described a case in which tooth #9 suffered a serious EIRR after intrusive luxation. The tooth was treated by REP. Eighteen-month periapical radiographs revealed progressive healing, EIRR arrestment, and remodeling of the lamina dura. Calcified deposits were observed in the root canal as well as a calcified bridge under the mineral trioxide aggregate. All these cases were treated by using a blood clot scaffold. The only case report that used PRF reported arrestment of internal root resorption and ERR[29]. The authors reported a 1-year follow-up with a positive response to thermal and electric pulp tests[29]. Collectively, these case reports suggest REPs as a viable alternative for the treatment of trauma-induced ERR.

Our case series shows clinical outcomes of 4 cases treated with REP since 2016. All teeth had a history of traumatic injuries and presented with significant ERR; ankylosis ensued in 3 of the 4 cases. All teeth at various stages of follow-up (12–30 months) showed resolution of signs and symptoms of apical periodontitis and were functional entities in the mouth. Moreover, in all teeth treated, EIRR was seen to be arrested after treatment. Moreover, in 3 cases, ankylosis was diagnosed preoperatively. In case 4, infraposition was diagnosed at the beginning of the treatment; however, no further advancement occurred after a 1-year follow-up (case 4). We did not observe reversal of RR in this case. A likely explanation for this could be that long-term treatment (7 months) with calcium hydroxide from another provider affected the outcome. On the other hand, cases 1 and 2 were diagnosed with ankylosis but did not develop infraposition throughout the follow-up period. Additionally, unlike case 4, in cases 1 and 2 ankylosis was seen to be reversed post-REP treatment. Therefore, a potential need for decoration and long-term temporary restoration were prevented[30,31].

To our knowledge, this is the first case series describing the beneficial role of REPs as a treatment modality for arresting detrimental sequelae of trauma-induced RR. Jung et al[32] states that although case series do not provide definitive evidence to support treatment modality, they have the advantage of being conducted in real patients and may provide future guidelines for prospective clinical trials.

It has recently been shown that stem cells of the apical papilla (SCAPs) are able to survive and retain their stemness despite inflammatory insults[29,33,34]. Moreover, SCAPs and other stem cell populations have been shown to be immunomodulatory[34]. Additionally, PRF has been shown to have several advantages over apical bleeding or a PRP scaffold[12,35]. Unlike PRP, PRF is strictly autologous. It needs no forward biochemical blood handling, and it is easy to prepare. PRP releases its growth factors within 24 hours, whereas PRF has a very significant slow sustained release of many key growth factors (eg, platelet-derived growth factor and transforming growth factor β for at least 1 week and up to 28 days[6]). Moreover, several lines of evidence suggest the superiority of PRF or PRP methods over an induced blood clot. A clinical study by Narang et al[35] compared MTA plug apexification, induced blood REP, REP with a PRF scaffold, and a scaffold of PRP with collagen. They concluded that “platelet-rich fibrin as a scaffold with concentrated micromolecules or storehouse of growth factors shows significant periapical healing, root lengthening, and dentinal wall thickening in necrotic immature permanent teeth over the blood clot and PRP.” Furthermore, a recently published meta-analysis also showed the superior outcomes of PRF over a blood clot[12]. We hypothesize that the combined effect of stem cells and their immunomodulation along with PRF likely explain the clinical outcomes observed in this study. Most articles lead to a conclusion that SCAPs as well as periodontal ligament stem cells after REP are recruited to penetrate into the root canal[36]. We speculate that there might be other ways that stem cells can spread after REP. As we attempt to achieve a sterile environment in the root canal, we reduce the leakage of toxic products into the periapical area. Moreover, appropriate dentin conditioning by chemicals such as EDTA and calcium hydroxide will expose the extracellular matrix (promoting cell adhesion) and trigger the release of embedded bioactive molecules (facilitating differentiation and proliferation)[14,37]. We assume that these bioactive molecules might find their way to the resorbed external root surface because it lacks any protective layer like cementum or periodontal ligament. This may lead to many changes including pH and may facilitate migration of stem cells into the affected root surface and initiate a repair process together with stems cells that migrated from the SCAPs and the periodontal ligament.

CONCLUSION

Our study adds a further layer to the few prior published case reports about arrestment of ERR by PRF. REP appears to be a promising modality for arresting ERR in young permanent teeth.

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The authors deny any conflicts of interest related to this study.

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