Different interventions and outcomes in four teeth with regenerative endodontic procedures in the same patient: A case report with 7-year follow-up

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Abstract. The present study reported on the case of a 10-year-old male patient with four second premolar teeth undergoing regenerative endodontic procedures (REPs) for periapical periodontitis due to abnormal central cusp fracture, and the follow-up over 7 years. Annual follow-up clinical and radiographic examinations were performed to assess the effectiveness of treatment. After the initial RPEs, the apical inflammation of teeth #15 and #45 disappeared and their roots continued to develop. However, teeth #25 and #35 exhibited different signs of inflammation and were treated with calcium hydroxide apexification and the second REPs, respectively. Subsequently, the narrowing of the apical foramen and healing of periapical inflammation were observed. The root of tooth #35 continued to develop but still exhibited apical inflammation. In the present case, apexification with calcium hydroxide and the second REPs were used as alternative interventions for teeth that failed after REPs. However, interventional treatment after a failure was not able to predict outcomes, necessitating a further study with a large number of cases for observational description.

Introduction

During tooth development, immature tooth pulp frequently becomes infected due to trauma, caries and the fracture of abnormal central cusps. The abnormal central cusp is a common malformation during tooth development. Previous studies have reported high frequencies of abnormal central cusps in mandibular second premolar teeth (1). During chewing and biting, the abnormal cusp is easily exposed to the pulp or dentinal tubules due to abrasion or fracture, resulting in pulp infection, necrosis and symptoms of periapical inflammation (2).

Due to incomplete root development with wide-open apical foramen, conventional root canal treatment in immature teeth with a necrotic pulp is not feasible. Typically, conventional apexification uses calcium hydroxide as an intracanal medicament to induce a hard tissue barrier and apical closure (3). An alternative treatment strategy in such cases is to create an artificial apical plug with the apical mineral trioxide aggregate (MTA) barrier technique (4). Although these treatments may eliminate the infection from the periapical tissues, the effects are limited. As a result, the root cannot continue to develop. In addition, root fractures are more common due to thin dentinal walls and an unfavorable crown-to-root ratio (5).

In 2012, the American Association of Endodontics (AAE) (6) listed regenerative endodontic procedures (REPs) in the treatment guidelines and recommended them for treating pulp necrosis of immature teeth (7). REPs are able to protect the vitality of undifferentiated mesenchymal stem cells as far as possible and provide a suitable microenvironment for the proliferation and differentiation of these stem cells to replace the dentin, cementum and pulp in the damaged tooth to promote root development and restore the vitality of the tooth pulp (8).

In recent years, REPs have been highly successful; however, certain failures have also been reported (9). Regarding alternative interventions after treatment failure, no reports are currently available, to the best of our knowledge. The present study reported on the 7-year follow-up of a 10-year-old male patient with four second premolar teeth subjected to REPs for periapical periodontitis due to fracture of abnormal central cusp.

Case report

A 10-year-old male patient presented to the Pediatric Dentistry Department of the Affiliated Hospital of Qingdao University (Qingdao, China) in August 2015 with spontaneous pain in the left mandibular second premolar tooth for one month. The left maxillofacial area had begun to swell one day previously.

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During the clinical evaluation, an extraoral examination revealed that the left maxillofacial area had a slight asymmetry and swelling. Intraoral examinations indicated the presence of a fractured abnormal central cusp on the left mandibular second premolar tooth. In addition, mild buccal vestibular swelling was observed. The abnormal central cusp of teeth #15, #25 and #45 had different degrees of wear. In the diagnostic tests, as the apical foramen is not yet formed in immature teeth, electric pulp testing is not applicable (10). The pulp vitality testing of teeth was performed using cold pulp testing. This technique is performed by drying the tooth surface, placing carbon dioxide snow on the buccal surface of the tested tooth and observing the patient's response (11). The same method was used to test normal adjacent teeth for comparison. Tooth #35 had significant pain on percussion and responded negatively to cold pulp tests using carbon dioxide snow, consistently with the normal adjacent teeth. At the time of probing the worn central cusps of the other second premolars, no perforations were found and the patient exhibited no signs of discomfort. Furthermore, teeth #15, #25 and #45 exhibited a sensitive positive response to the cold pulp testing, consistently with the normal teeth. Radiographically, tooth #35 had an open apex with periapical radiolucency. Pulpal necrosis with periapical periodontitis was the final diagnosis based on the clinical presentation. After explaining the treatment plan, risks and benefits to the parents, they selected REP on tooth #35. Since teeth #15, #25 and #45 were not clinically symptomatic and exhibited pulp vitality, a treatment plan using composite resin to protect the abnormal central cusps was recommended. However, the patient was too young to cooperate in completing the treatment and the patient's parents decided to temporarily abandon the preventive treatment and have regular follow-up observations.

At the first treatment appointment, the root canal debridement was completed after local anesthesia and rubber dam isolation. The root canal system was irrigated thoroughly and slowly with 20 ml of 1.5% sodium hypochlorite solution (Longly Biotechnology Co., Ltd), followed by 20 ml of sterile saline solution for 5 min. After irrigation, the root canals were dried with absorbent paper points (Dayading Co., Ltd) prior to being filled with creamy calcium hydroxide (Pulpdent Corp.). Subsequently, Cavit (3M ESPE Dental Products) was used to seal the access cavity as a temporary restoration and the procedure was repeated one week later.

At the second appointment, the facial swelling had disappeared and there was no sensitivity to percussion in the clinical examination. After isolating with a rubber dam and removing the temporary sealing material, the interim intracanal medicament was irrigated with 1.5% sodium hypochlorite (Longly Biotechnology Co., Ltd) with ultrasonic agitation for 20 sec each time, 3 times in total (frequency, 28-35 kHz; power, 10 W). A creamy mix of triple antibiotic paste was prepared by mixing 50 mg of each of ciprofloxacin (Jiangbo Co., Ltd), metronidazole (Kangmei, Inc.) and amoxicillin (Hengshan Pharm Co., Ltd) with 1 ml of saline solution. After irrigating the root canal with saline solution and drying it with paper points, the triple antibiotic paste was placed into the root canal. Cavit was used as a temporary sealant of the access cavity and an appointment was made for a return visit two weeks later.

At the third appointment, the patient was asymptomatic. Local anesthesia was achieved using an inferior alveolar nerve block with 3% mepivacaine plain (SEPTODONT, Inc), followed by rubber dam isolation. After flushing with 1.5% sodium hypochlorite with thorough ultrasonic agitation for 20 sec each time, 3 times in total (ultrasonic frequency, 28-35 kHz; power, 10 W), no significant bleeding or inflammatory exudation were observed. The filing was then overextended to induce bleeding by irritating the periapical tissues so that the blood entered the root canal system. Following the formation of a stable blood clot, it was covered with a coating of light-cured calcium hydroxide (Pulpdent Corp.) and composite resin (3M ESPE Dental Products Division) was used to reconstruct the tooth.

However, the other second premolars developed symptoms during the REP for tooth #35. The diagnosis was symptomatic apical periodontitis of varying degrees, accompanied by the symptoms of infection in the maxillofacial space. After consultation with the patient's parents, the remaining teeth were treated with REPs. At each follow-up visit, periapical radiographs of the affected teeth were acquired (Figs. 1-4). All periapical radiographs were taken using a Minray (Soredex) at 5 mA and 70 kV with an exposure time of 0.12 sec. The periapical radiographs were calibrated using Turboreg (Biomedical Imaging Group, Swiss Federal Institute of Technology) which is a plug-in for Image J software (version 1.41; National Institutes of Health) to reduce the bias caused by variations in the projection angle (12). Subsequently, the changes in root length, apical foramen size and radiographic root area (RRA) (13) were measured using Image J software to quantitatively analyze the tooth root development (Tables I-III). The same researcher took all the measurements and the average of three measurements was used to report the final value. A 20% cut-off was set as a clinically meaningful threshold in the radiographic variables (14,15).

At the one-year follow-up visit, the clinical symptoms of teeth #15 and #45 had completely disappeared and the responses to cold pulp testing were negative. The X-ray film indicated an increase in root length, as well as a narrowing of the root canal width and the apical foramen, all of which indicated that the root was still developing (Figs. 1B and 4B). The REPs for teeth #15 and #45 were effective, and since the roots were not mature, it was decided to continue follow-up observations of these teeth without further treatment and consider root canal treatment when root development was completed. A sinus tract associated with tooth #35 was observed (Fig. 3B). After consultation with the parents, the second REPs were performed. In addition to repeating the previous procedure, as recommended by the AAE (6), 20 ml of 1.5% sodium hypochlorite was used for irrigation, followed by 20 ml of 17% EDTA for 5 min during root canal disinfection. Meanwhile, when the other teeth were examined, tooth #25 was painful, indicating periapical inflammation (Fig. 2B). Apexification with calcium hydroxide was performed to avoid further extension of periapical inflammation (Fig. 2C). When the apical foramen of tooth #25 was closed, it was treated with conventional endodontic treatment, which entailed adequate cleaning, shape and filling.

In the three-year follow-up, the root development of teeth #15, #25, #35 and #45 was basically complete (Figs. 1D, 2D, 3D and 4D). At the five-year follow-up visits, cone-beam computed tomography (CBCT) examinations were performed

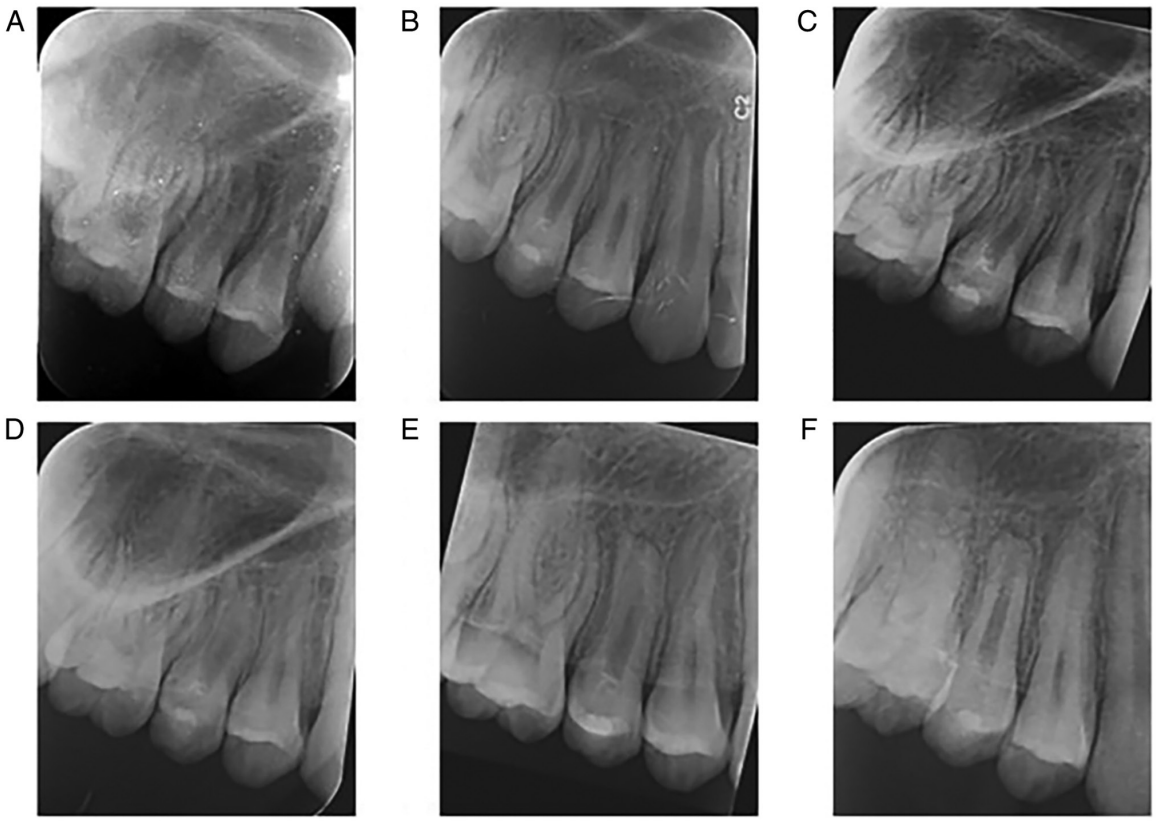

Figure 1. Follow-up periapical radiographs of tooth #15. (A) Preoperative radiograph. (B-F) follow-up radiograph after REPs at (B) 1 year, (C) 2 years, (D) 3 years, (E) 4 years and (F) 5 years. REPs, regenerative endodontic procedures.

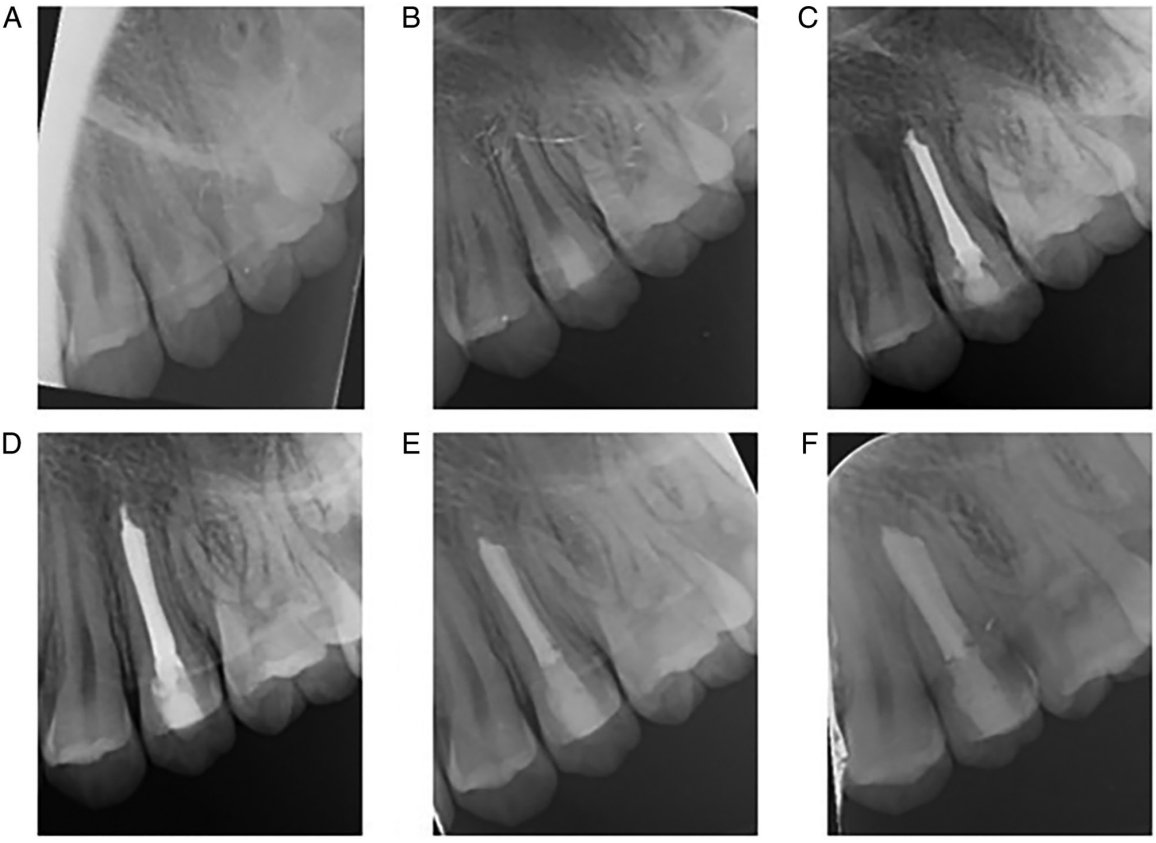

Figure 2. Follow-up periapical radiographs of tooth #25. (A) Preoperative radiograph. (B) 1-year follow-up radiograph after REPs; tooth #25 was treated by apexification with calcium hydroxide. (C) 1-year follow-up after conventional apexification, tooth #25 was subjected to conventional endodontic treatment. (D) 2-year, (E) 3-year and (F) 4-year follow-up after conventional apexification. REPs, regenerative endodontic procedures.

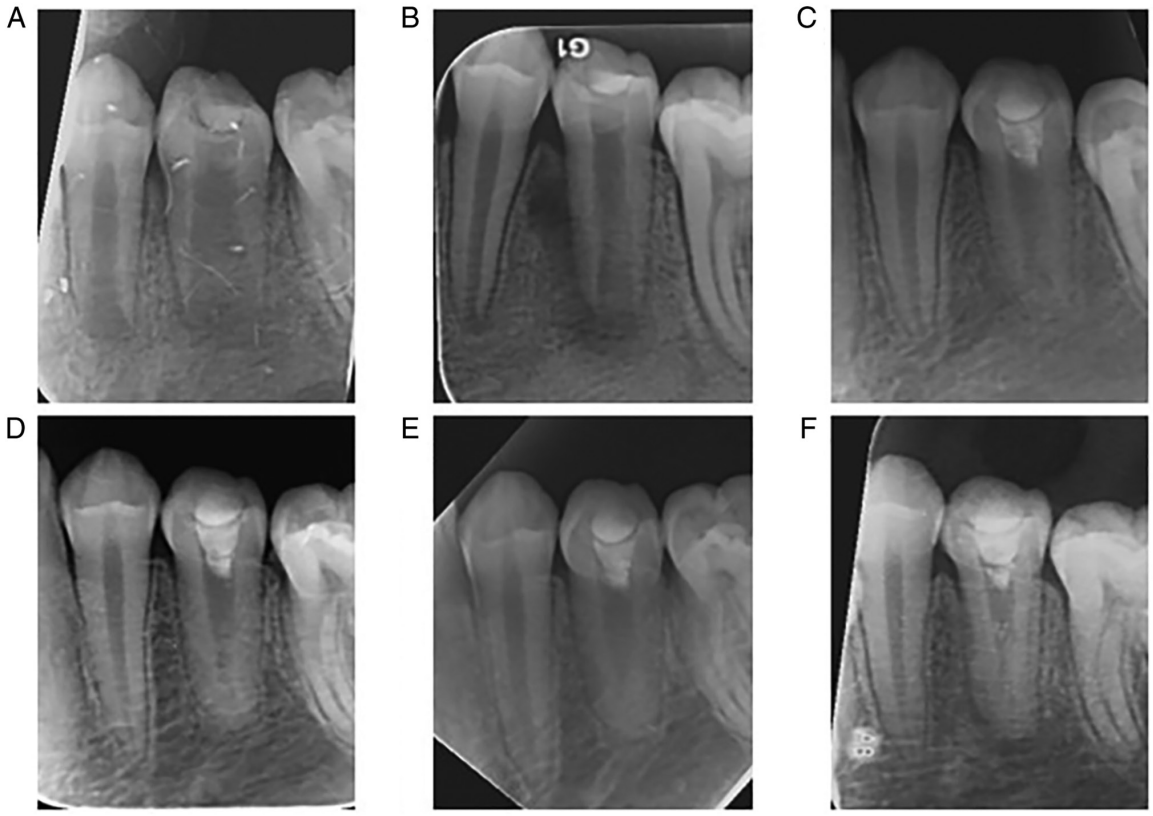

Figure 3. Follow-up periapical radiographs of tooth #35. (A) Preoperative radiograph. (B) 1-year follow-up radiograph after REP; tooth #35 was treated with the second REP. (C) 1-year, (D) 2-year, (E) 3-year and (F) 4-year follow-up radiograph after the second REP. REPs, regenerative endodontic procedure.

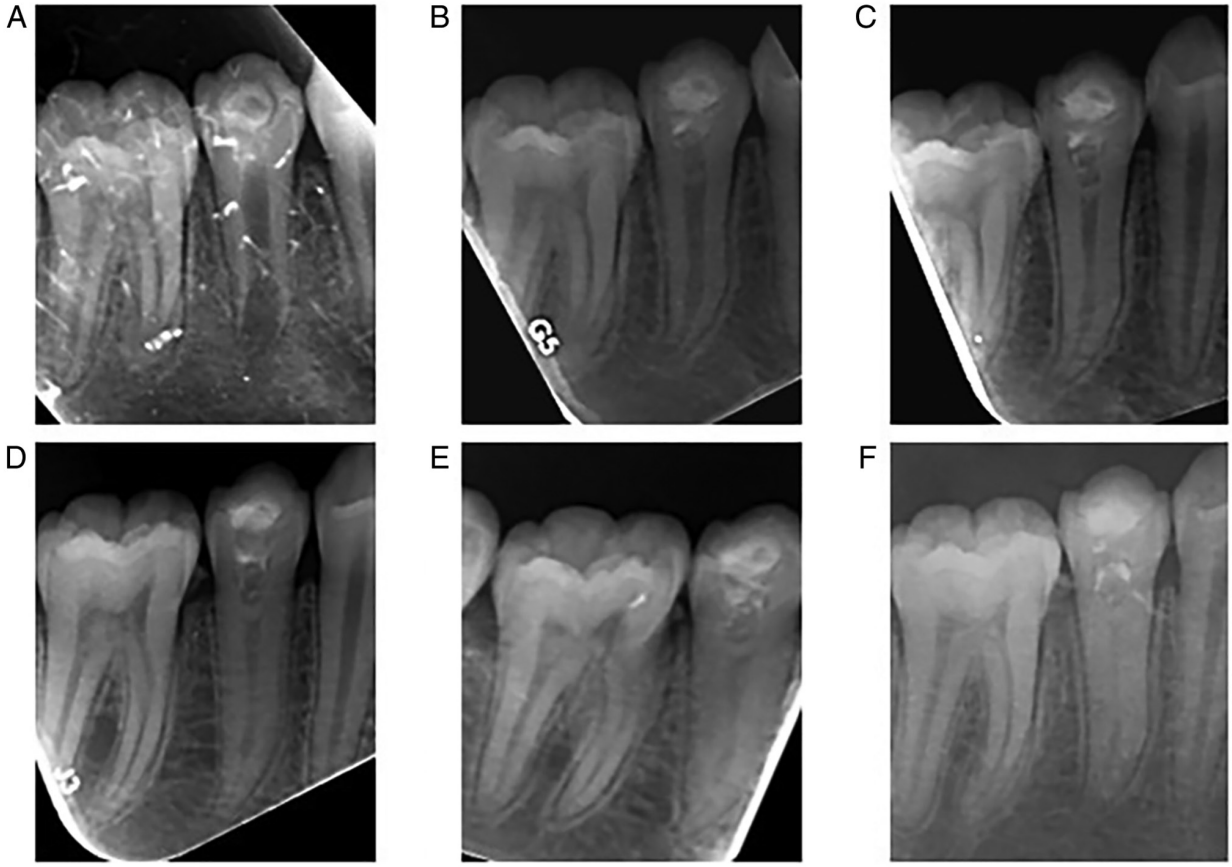

Figure 4. 5-year follow-up periapical radiographs of tooth #45. (A) Preoperative radiograph. (B) 1-year, (C) 2-year, (D) 3-year, (E) 4-year and (F) 5-year follow-up radiograph after the regenerative endodontic procedure.

Table I. Changes in the radiographic root area of the affected tooth before and after regenerative endodontic procedures (%).

Tooth ID	12 M	24 M	36 M	48 M	60 M
#15	50.65	67.98	77.12	84.11	84.66
#25	20.10	20.61	32.70	33.30	33.38
#35	70.67	98.02	110.48	112.88	114.04
#45	34.99	72.42	81.36	81.59	81.20

M, months.

Table II. Changes in the root length of the affected tooth before and after regenerative endodontic procedures (%).

Tooth ID	12 M	24 M	36 M	48 M	60 M
#15	20.98	21.65	30.92	31.67	31.14
#25	5.96	11.20	12.35	13.92	13.84
#35	20.12	26.34	27.10	27.98	28.15
#45	14.89	29.88	29.91	30.11	30.75

M, months.

Table III. Changes in the apical foramen of the affected tooth before and after regenerative endodontic procedures (%).

Tooth ID	12 M	24 M	36 M	48 M	60 M
#15	38.52	61.97	68.25	69.45	72.46
#25	19.90	39.53	79.36	81.70	81.84
#35	45.40	59.08	82.34	100	100
#45	47.50	70.00	76.64	78.32	78.56

M, months.

to better observe the development of the roots of the affected teeth (Fig. 5A-D). All CBCT images were acquired using an iCAT 17-19 (KaVo) set at 5 mA and 120 kV with an exposure time of 14.7 sec with a voxel size of 0.25 mm. Tooth #35 still had a small periapical radiolucency but the patient had no other symptoms and was scheduled for regular visits. The patient was unable to have a follow-up visit in the sixth year due to being away at school. In the seventh year, the patient was seen again for an examination of the affected teeth. The patient was re-examined by CBCT and it was found that the other affected teeth remained stable with no significant changes; however, the size of periapical radiolucency of #35 was enlarged (Fig. 5E-H). Since the root was developed, prompt root canal treatment was recommended.

Discussion

According to the objectives of REPs described by the AAE and Geisler (16), the primary goal is to eliminate the symptoms and promote periapical healing in the affected tooth. The second goal is to induce root canal wall thickening and root lengthening. The third goal is to elicit a positive response to the pulp vitality tests, which indicates pulp tissue regeneration. In the present case, the primary and secondary objectives were achieved in teeth #15 and #45. The REPs of teeth #25 and #35 had unfavorable outcomes. However, a thickening of the canal walls, apical closure and prolongation of the root was observed. The European Society of Endodontology (ESE) lists the above three objectives as the success criteria for REPs (17). Wei *et al* (18) concluded that the positive responses of pulp vitality tests after REPs may be a false-positive reaction of the tissue in the root canal due to the affected vessels and nerves, necessitating histological studies to confirm pulp tissue regeneration. Therefore, the evaluation of the success of REPs according to the AAE is more appropriate for clinical assessments.

Concerning previous studies on REPs with follow-ups and qualitative analyses, Chan *et al* (19) reported an average increase of 8.1% in root length, a 34% decrease in apical diameter and increase of 11.6% in RRA per tooth during the 30-month follow-up. A previously published systematic review indicated only 16.1% of root lengthening, 39.8% of root thickening, a 34.9% increase in RRA and a 90.7% increase in incidence of apical closure when 20% of the radiographic changes were used as cut-off points (20). Similar to previous studies, significant changes were detected. The RRA changes of teeth #15, #25, #35 and #45 reached a threshold at one year after the treatment and gradually increased at the follow-ups, remaining stable after the third year of treatment. However, from the periapical radiograph, the change in root length and the size of the apical foramen were most significant three years after treatment, which remained stable during the later follow-up.

During the follow-up, it was revealed that the REPs had unfavorable outcomes in teeth #25 and #35. In chronic inflammatory reactions in the periapical area, it was not possible to control the inflammatory process in the root canals and the long-term inflammatory environment led to failure of the REPs. The main reason for failure in these cases was the bacterial residue after root canal disinfection and cleaning. In the process of REPs, bacteria in the root canals are able to survive in locations that are difficult to reach by disinfecting agents, resisting chemical disinfection to cause reinfection of the root canal (21). The commonly used clinical root canal disinfectant is a 1-5 mg/ml antibiotic dressing, as recommended by the AAE (6). For the present case, the AAE guidelines were also followed. The triple antibiotic paste was used as the intra-canal medicament, which is more effective than calcium hydroxide (22). In addition, in a large number of previous cases, it was found that triple antibiotics had a better antibacterial capacity and lower likelihood of root canal calcification than calcium hydroxide. However, it has the disadvantages of tooth discoloration, toxicity to stem cells of the apical papilla (SCAP) and difficulty of removal from the root canal (23,24). Calcium hydroxide does not have these disadvantages and is the preferred root canal medicament recommended by the ESE (17). It has been suggested that in persistent infections, extended disinfection times to achieve complete disinfection may lead to successful treatment outcomes (25). The second

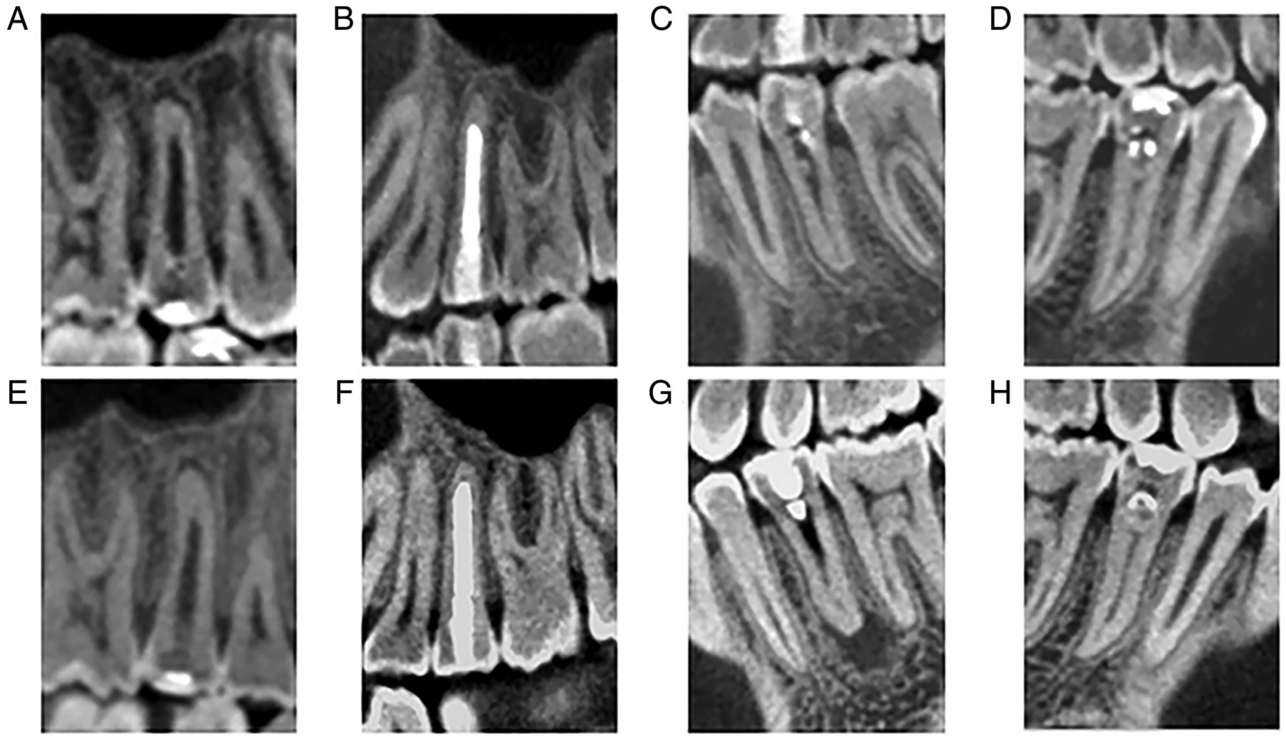

Figure 5. Follow-up CBCT after REPs. 5-year follow-up CBCT after REPs of teeth (A) #15, (B) #25, (C) #35 and (D) #45. 7-year follow-up radiograph after REPs of teeth (E) #15, (F) #25, (G) #35 and (H) #45. REPs, regenerative endodontic procedures; CBCT, cone-beam computed tomography.

REPs of tooth #35 ended in apical inflammation despite enhanced endodontic disinfection, which may be attributed to residual bacteria in the root canal that are resistant to the currently available disinfecting agents. Therefore, the bacteria in the root canals of teeth with failed REPs require to be further studied to propose a new disinfection protocol.

There is still a lack of extensive literature on cases of failed REP. A current systematic review (26) analyzed 67 cases of REP failure and indicated that in most cases of failed REP, MTA apical induction angioplasty had been opted for, while the remaining cases were treated by conventional endodontic techniques, apical induction angioplasty or the second REPs. The cases associated with the second REPs all exhibited enhanced disinfection of the root canal, either by application of calcium hydroxide in the root canal (27) or a combination of 2% chlorhexidine and calcium hydroxide with antimicrobial properties as an intracanal medicament (28). Follow-up examinations revealed significant healing of periapical lesions, apical foramen narrowing and root maturation.

In the present case, different interventions were selected depending on the root development of teeth #25 and #35 after the failure of the first REPs. The second REP was performed for tooth #35 with a large root canal apical and thin root canal wall. Root formation depended on the odontogenic differentiation of SCAPs induced by Hertwig's epithelial root sheath (HERS). Since the apex is wider and the number of apical stem cells of the former is higher, the success rate of REPs is higher for teeth with undeveloped roots. Therefore, the size of the apical foramen may affect the postoperative success of the second REPs (29). For cases where the apical foramen is too small to provide an abundant blood supply, the AAE recommends the use of platelet-rich plasma, platelet-rich fibrin or autologous fibrin matrix as an alternative stent scaffold (6). In addition, the survival rate of HERS and SCAPs is affected by the duration and severity of the inflammatory reaction in the periapical tissue and the sustained inflammatory signaling in the root canal may interfere with the differentiation and maturation of SCAPs, leading to the retardation of root development (30-32). The success rate of the second REPs may be lower than that of the initial attempt due to the risk of damage to the apical papilla and HERS during the previous sterilization process. To the best of our knowledge, no previous reports have suggested factors affecting the success of the second REPs.

Regular follow-up of the pulp after REPs is essential. In the present case, teeth #25 and #35 exhibited inflammatory symptoms one to two years after the completion of treatment. The failure of the second REPs was observed in tooth #35 at the 7-year follow-up. A systematic review reported that the time from the initiation of REPs to confirmation of failure cases ranged from 3 weeks to 8 years (26). One study indicated that the success rate of REPs decreased from 87 to 77% at follow-ups, ranging from 24 to 36 months (33). The success rate of the treatment gradually decreased over time. Therefore, it is recommended that if the root is almost or fully developed and resistant to fracture, a complete root canal treatment may be considered to avoid the possible residual bacteria in the root canal that may cause a recurrence of apical inflammation. In addition, although it is difficult to ask the patient and their parents to attend regular follow-up sessions, it is necessary to strongly emphasize the importance of regular visits to discover signs of failure in teeth that require further treatment.

In summary, REPs are able to promote root development of in immature teeth, with important applications in young

patients. After the failure of REP, other interventions are available to promote apical inflammation regression after enhancing root canal disinfection. Calcium hydroxide apexification or the second REPs may be alternative interventions for teeth with an unfavorable outcome after REPs. It is required to further describe alternative interventions to provide recommendations with precision and predictability for alternative interventions after failure.

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Availability of data and material

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

JYa and XHG performed the literature search/selection/review, collected clinical information and drafted the manuscript. RH provided critical pathological reports and diagnostic consulting. LBX collated the figures and data. LM conceived the study and revised the manuscript. JYu analysed and interpreted the data and figures. JYu and LM confirm the authenticity of all the raw data. All authors have read and approved the final manuscript.

Ethics approval and consent to participate

This study was approved by the Human Research Ethics Committee of The Affiliated Hospital of Qingdao University (approval no. QYFY WZLL 26895).

Patient consent for publication

Written consent for publication of the patient's data/images in this case report was obtained from a parent of the patient.

Competing interests

The authors declare that they have no competing interests.

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