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Short-term vs long-term calcium hydroxide therapy after immediate tooth replantation: a histomorphometric study in monkey's teeth

Sônia Regina Panzarini[1], Jéssica Lemos Gulinelli[1], Célia T. M. H. Saito[1], Wilson Roberto Poi[1], Celso Koogi Sonoda[1], José Américo de Oliveira[2], Moriel Evangelista Melo[1], Weglis Dyanne de Souza Gomes[1]

[1]Department of Surgery and Integrated Clinics, School of Dentistry of Araçatuba, Universidade Estadual Paulista (UNESP), Araçatuba; [2]Department of Basic Sciences, School of Dentistry of Araçatuba, Universidade Estadual Paulista (UNESP), Araçatuba, Brazil

Correspondence to: Sônia Regina Panzarini, Faculdade de Odontologia de Araçatuba, UNESP, Disciplina de Clínica Integrada, Rua José Bonifácio, 1193, Bairro Vila Mendonça, 16015-050 Araçatuba, SP, Brazil
Tel.: +55 18 3636 3240
Fax: +55 18 3636 3332
e-mail: panzarin@foa.unesp.br

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Abstract – Endodontic treatment is an important step of tooth replantation protocols, but the ideal moment for definitive obturation of replanted teeth has not yet been established. In this study, a histomorphometric analysis was undertaken to evaluate the repair process on immediate replantation of monkey's teeth after calcium hydroxide (CH) therapy for 1 and 6 months followed by root canal filling with a CH-based sealer (Sealapex®). The maxillary and mandibular lateral incisors of five female Cebus apella monkeys were extracted, kept in sterile saline for 15 min, replanted and splinted with stainless steel orthodontic wire and composite resin for 10 days. In Group I (control), definitive root canal filling was performed before tooth extraction. In Groups II and III, CH therapy started after removal of splint, and definitive root canal filling was performed 1 and 6 months later, respectively. The animals were euthanized 9 months after replantation, and specimens were processed for histomorphometric analysis. In all groups, epithelial attachment occurred at the cementoenamel junction or very close to this region; the areas of resorption on root surface had small extension and depth and were repaired by newly formed cementum; and the periodontal ligament was organized. Statistical analysis of the scores obtained for the histomorphometric parameters did not show any statistically significant difference ($P = 0.1221$) among the groups. The results suggests that when endodontic treatment is initiated 10 days after immediate replantation and an antibiotic regimen is associated, definitive root canal filling can be performed after a short-term CH therapy.

Immediate replantation of traumatically avulsed teeth offers more favorable conditions for repair to occur because the vitality of the periodontal ligament (PDL) cells is preserved and the chance of reattachment of PDL fibers is increased (1–3).

Controlling the inflammatory process during the periodontal healing is a key factor in replantation procedures because root resorption is classically described as resulting from long standing acute or chronic inflammation (3). Antibiotic therapy and endodontic treatment are also recommended because bacterial infection of endodontic or periodontal origin can be installed in replanted teeth (3–6).

Traditionally, the clinical management of avulsed teeth with closed apex included endodontic treatment being started 7–10 days after replantation with long-term calcium hydroxide (CH) therapy (6–12 months) before definitive root canal filling (5, 7). More recent protocols have stated that a CH intracanal medication should be used during 1 month and then the definitive obturation can be performed as long as the endodontic therapy had been started 7–14 days after replantation and an inflammatory resorption process had not developed (8).

As the ideal moment for definitive obturation of replanted teeth after medication with a CH intracanal dressing has not yet been established, a histomorphometric analysis was undertaken in this study to evaluate the repair process on immediate replantation of monkey's teeth after short-term (1 month) and long-term (6 months) CH therapy and root canal filling with a CH-based sealer.

Material and methods

Five adult female *Cebus apella* monkeys weighing 2–3 kg were obtained from the Capuchin Monkey Procreation Center at the School of Dentistry of Araçatuba, UNESP, Brazil, for this study. The research protocol was approved by the local Animal Care and Use Committee (protocol number 008837-2009) and all guidelines regarding the care of animal research subjects were strictly followed. The animals were maintained in individual cages and received food and water *ad libitum* during the entire experiment.

The animals were weighed and received intramuscular injections of ketamine hydrochloride (15 mg kg^{-1} body

weight, Dopalen®; Agribrands do Brasil LTDA, Paulínea, SP, Brazil) and benzodiazepine (0.1 ml kg^{-1} body weight, Diazepan®; Sigma Pharma, São Bernardo do Campo, SP, Brazil) to promote sedation and muscular relaxation, respectively, and were anesthetized with an intraperitoneal injection of sodium thiopental (30 mg kg^{-1} body weight, Thionembutal®; Abbott Laboratórios do Brasil LTDA, São Paulo, SP, Brazil). To promote local anesthesia and hemostasis of the operative field, the animals received a local infiltration of 2% mepivacaine hydrochloride (2% Scandicaine with 1:100 000 adrenaline, Septodont, Saint-Maur-des-Fossés France). The following groups were formed:

Group I (control; one animal) – after placement of a rubber dam and cleaning of the operative filed with 1% iodine polyvinylpyrrolidone (Riodeine; Indústria Farmacêutica Rioquímica Ltda., São José do Rio Preto, SP, Brazil), four maxillary and mandibular lateral incisors were treated endodontically. In each tooth, the access cavity was prepared on the palatal/lingual face with diamond burs in a high-speed handpiece under continuous irrigation with distilled water. The pulp tissue was extirpated with a size 15 K-file (Sybron Kerr Corporation, Orange, CA, USA) and the coronal and middle thirds of the canals were preflared with orifice openers (Maillefer, Ballaigues, Switzerland) and Gates-Glidden drills (Maillefer, Ballaigues, Switzerland). The root canal were prepared in a crown-down approach with a sequence of K-files up to size 35 at 1 mm short of the apex followed by Hedström files (Maillefer, Ballaigues, Switzerland), being irrigated with a CH/distilled water suspension at each change of file. After instrumentation, fluid was aspirated and the canals were dried with absorbent paper points and filled with gutta-percha cones and a CH-based sealer (Sealapex; Kerr Corporation, Orange, CA, USA) according to the lateral compaction technique. The coronal access was sealed with chemically cured glass ionomer cement (Vidrion R; SS White, Rio de Janeiro, RJ, Brazil). The root-filled teeth were extracted and immersed in 20 ml of saline (Ariston Ind. Quim. and Farm. Ltda, São Paulo, SP, Brazil) for 15 min. After gentle irrigation of the alveolar wounds with sterile saline, the teeth were replanted and splinted with 0.7 mm stainless steel orthodontic wire (Dental Morelli Ltda., Sorocaba, SP, Brazil) and light-activated composite resin (TPH-Spectrum; Dentsply DeTrey, Konstanz, Germany) for 10 days.

Group II (two animals) – eight maxillary and mandibular lateral incisors were extracted, maintained in saline for 15 min, and then replanted and splinted for 10 days, as described in Group I. After removal of the splint, the endodontic treatment was initiated in the same as described for Group I, except for the use of an intracanal dressing before obturation. The instrumented canals were filled with a CH-based paste (5 ml propylene glycol, 5 g of GH, 2 g zinc oxide, 0.015 g colophony; Discipline of Endodontics, School of Dentistry of Araçatuba, UNESP, Araçatuba, Brazil) packed in anesthetic cartridges using a G27 blunt-end needle attached to a Carpule syringe (Terumo Corporation, Tokyo, Japan). The intracanal dressing was maintained for 1 month and then definitive root canal filling was performed as described in Group I.

Group III (two animals) – eight maxillary and mandibular lateral incisors received the same treatment described for Group II, except that the intracanal dressing was maintained for 6 months before definitive root canal filling, with change of the medication at 3 months.

After extraction and replantation procedures, the animals received the following medications diluted in the food: amoxicillin (20 mg kg^{-1}, three times a day, during 7 days; Laboratórios Stiefel Ltda., Guarulhos, SP, Brazil), sodium diclofenac (30 mg kg^{-1}, twice a day, during 7 days; Laboratório Delta, Carazinho, RS, Brazil), and paracetamol (30 mg kg^{-1}, once a day, during 2 days, Tylenol®; Janssen-Cilag, São José dos Campos, SP, Brazil).

Euthanasia was performed 9 months after replantation. The animals were anesthetized with ketamine hydrochloride (15 mg kg^{-1}, i.m.) followed by sodium pentobarbital (30 mg kg^{-1}, i.p.) and then transcardially perfused with 0.9% saline (800 ml) followed by 1500 ml of 4% paraformaldehyde in 0.1 M acetate buffer, pH 6.5, and subsequently by 1500 ml of 4% paraformaldehyde in 0.1 M borate buffer, pH 9.0. The anatomic blocks containing the replanted teeth were removed, fixed in 10% neutral formalin for 48 h and decalcified in a 17% EDTA solution for approximately 90 days. After this period, the specimens were embedded in paraffin and longitudinal 6-μm-thick serial sections were obtained, in such a way that the entire extension of the PDL and alveolar bone could be visualized, and were stained with hematoxylin and eosin for histomorphometric analysis under optical microscopy.

Analysis of the outcomes was performed by one of the authors in a blind fashion, according to the 16 histomorphometric parameters listed below, which received scores 1–4, 1 being the best result and 4 the worst, with intermediate outcomes for scores 2 and 3 (9). This list of histomorphometric parameters can be used to immediate and delayed tooth replantation studies, and therefore, some of the attributed scores apply only to one or another condition.

1 Area of epithelial attachment
  1. cementoenamel junction;
  2. ligament below the cementoenamel junction;
  3. much below the cementoenamel junction (near the middle third);
  4. absence of epithelial attachment.

2 Acute and chronic inflammatory process close to the area of epithelial attachment
  2.1. Intensity of inflammatory process based on the criteria described by Wolfson and Seltzer (10)
    1. absence or occasional presence of inflammatory cells;
    2. small number of inflammatory cells (≤10 cells per field with 400× magnification);
    3. moderate number of inflammatory cells (11–50 cells per field with 400× magnification);
    4. large number of inflammatory cells (> 50 cells per field with 400× magnification).
  2.2. Extension of the inflammatory process
    1. absence or occasional presence of inflammatory cells;

2. inflammatory process restricted to the lamina propria of the internal aspect of the epithelium;
3. inflammatory process extending apically toward the small portion of connective tissue underlying the lamina propria of the internal aspect of the gingival epithelium;
4. inflammatory process reaching the area near the alveolar bone crest.

3 PDL
- 3.1. PDL organization
  1. PDL fibers inserted in bone and cementum throughout the ligament extension;
  2. PDL fibers inserted in bone and cementum at two-thirds of the ligament extension;
  3. PDL fibers inserted in the bone and cementum at one-third of the ligament extension;
  4. absence of PDL fibers with insertion in bone and cementum.
- 3.2. Intensity and extension of acute and chronic inflammatory process in the PDL.
  - 3.2.1 Intensity – same criteria used for the area of epithelial attachment.
  - 3.2.2 Extension of the inflammatory process.
    1. absence or occasional presence of inflammatory cells;
    2. inflammatory process present only in the apical or coronal PDL or in a small are of the lateral PDL;
    3. inflammatory process reaching more than half of the lateral PDL;
    4. inflammatory process in the entire PDL extension.

4 Tooth root
- **4.1 Active and inactive root resorption**
  1. absence of root resorption or repaired resorptions;
  2. areas of inactive resorption (absence of clastic cells);
  3. small areas of active resorption;
  4. extensive areas of active resorption.
- **4.2** Extension of root resorption – the diameter of the resorbed areas was measured (in micrometers) in representative sections. The mean of the values obtained on the buccal and lingual aspects allowed assignment of the following scores:
  1. absence of resorption;
  2. mean extension of 1–1000 μm;
  2. mean extension of 1001–5000 μm;
  4. mean extension ≥5001 μm.
- **4.3** Depth of root resorption – the depth of the resorption areas was measured (in micrometers) in representative sections. The mean of the values obtained on the buccal and lingual aspects allowed assignment of the following scores:
  1. absence of resorption;
  2. mean depth of 1–100 μm;
  3. mean depth of 101–200 μm;
  4. mean depth ≥201 μm;
- **4.4.** Repair of root resorption areas.
  1. absence of resorption or deposition of newly formed cementum throughout the extension of the resorbed areas;
  2. deposition of newly formed cementum in half or more of the extension of the resorbed areas;
  3. deposition of newly formed cementum in less than half of the resorbed areas;
  4. absence of deposition of newly formed cementum in the resorbed areas.

5 Bone tissue – areas of active and inactive resorption
1. absence of resorption areas;
2. presence of inactive resorption areas (absence of clastic cells);
3. presence of small areas of active resorption;
4. presence of extensive areas of active resorption.

6 Ankylosis
1. absence of ankylosis;
2. small areas of ankylosis;
3. one-third of the root with ankylosis;
4. more than one-third of the root with ankylosis.

Data were subjected to statistical analysis by the Kruskal–Wallis test to assess the differences found in each parameter and the characteristics of each group. The significance level was set at 5%.

Results

The distribution of the scores according to the histomorphometric parameters in each group is detailed in Table 1.

Group I (control) – root canal filling before extraction

In all specimens, epithelial attachment occurred at the cementoenamel junction, with no signs of inflammation in the adjacent connective tissue. The PDL was organized, with no inflammatory cells, and PDL fibers were arranged perpendicular to the root surface and attached along the entire extension of the alveolar bone and cementum (Fig. 1). Small areas of surface root resorption were observed in most specimens, with the presence of cementoblasts depositing newly formed cementum close to the root surface (Fig. 2).

Group II – root canal filling 1 month after replantation

In all specimens, epithelial attachment occurred at the cementoenamel junction, with no signs of inflammation in the adjacent connective tissue. Small and shallow resorptive areas on the cemental surface of the root were observed (Fig. 3). The PDL was organized, with no signs of inflammation and fibers arranged perpendicular to the root surface. Epithelial rests of Malassez were present, indicating PDL regeneration (Fig. 4).

Group III – root canal filling 6 months after replantation

Epithelial attachment occurred at the cementoenamel junction in most specimens and slightly below this region

Table 1. The distribution of the scores according to the histomorphometric parameters in each group

	Group I				Group II				Group III			
	Score				Score				Score			
Histomorphometric parameters	1	2	3	4	1	2	3	4	1	2	3	4
Epithelial attachment												
Area	4/4	0/4	0/4	0/4	8/8	0/8	0/8	0/8	8/8	0/8	0/8	0/8
Inflammatory infiltrate												
Acute												
Intensity	4/4	0/4	0/4	0/4	8/8	0/8	0/8	0/8	8/8	0/8	0/8	0/8
Extension	4/4	0/4	0/4	0/4	8/8	0/8	0/8	0/8	8/8	0/8	0/8	0/8
Chronic												
Intensity	3/4	1/4	0/4	0/4	8/8	0/8	0/8	0/8	8/8	0/8	0/8	0/8
Extension	3/4	1/4	0/4	0/4	8/8	0/8	0/8	0/8	8/8	0/8	0/8	0/8
Periodontal ligament												
Organization	4/4	0/4	0/4	0/4	8/8	0/8	0/8	0/8	8/8	0/8	0/8	0/8
Inflammatory infiltrate												
Acute												
Intensity	4/4	0/4	0/4	0/4	8/8	0/8	0/8	0/8	8/8	0/8	0/8	0/8
Extension	4/4	0/4	0/4	0/4	8/8	0/8	0/8	0/8	8/8	0/8	0/8	0/8
Chronic												
Intensity	4/4	0/4	0/4	0/4	8/8	0/8	0/8	0/8	8/8	0/8	0/8	0/8
Extension	4/4	0/4	0/4	0/4	8/8	0/8	0/8	0/8	8/8	0/8	0/8	0/8
Root resorption												
Active/inactive	4/4	0/4	0/4	0/4	3/8	5/8	0/8	0/8	7/8	1/8	0/8	0/8
Extension	1/4	3/4	0/4	0/4	3/8	5/8	0/8	0/8	7/8	1/8	0/8	0/8
Depth	1/4	3/4	0/4	0/4	3/8	5/8	0/8	0/8	7/8	1/8	0/8	0/8
Repair	1/4	1/4	2/4	0/4	4/8	4/8	0/8	0/8	7/8	1/8	0/8	0/8
Bone tissue												
Resorption	4/4	0/4	0/4	0/4	8/8	0/8	0/8	0/8	8/8	0/8	0/8	0/8
Ankylosis	4/4	0/4	0/4	0/4	8/8	0/8	0/8	0/8	7/8	1/8	0/8	0/8

In Group I (control), definitive root canal filling was performed before tooth extraction. In Groups II and III, CH therapy started after the removal of splint, and definitive root canal filling was performed 1 and 6 months later, respectively.

in some specimens. No chronic or acute inflammatory process was observed in the subjacent connective tissue. The PDL was organized, with the absence of inflammatory cells and fibers arranged perpendicular to the root surface. The PDL space was preserved. Some resorbed areas on root surface were repaired by newly formed cementum (Fig. 5). Replacement root resorption was observed in only one specimen (Fig. 6).

Statistical analysis of the scores attributed to the histomorphometric parameters did not show any significant difference ($P = 0.1221$) among the groups.

Discussion

The viability of remaining PDL cells and its mechanism of repair are intimately related to the extra-alveolar time, handling of the avulsed tooth and the storage medium in which the tooth is maintained until replantation is performed (3, 8, 10).

In the present study, the vitality of the PDL cells was preserved after storage of the extracted teeth in sterile saline for 15 min, permitting repair of the PDL with reattachment of its fibers to alveolar bone and cementum in all groups. Such an extra-alveolar time was waited because under clinical conditions, a tooth hardly ever is replanted immediately after avulsion and some time usually elapse until replantation is carried out.

After replantation, healing can occur by PDL regeneration or repair followed by surface root resorption, replacement root resorption, or inflammatory root resorption. The vitality and contamination of the cemental PDL cells are main factors that interfere directly with the healing process are (1–3). If the tooth is transferred to a liquid medium such as saline within the first 15 min, some of the cells in the PDL and cementum will survive and may play a role in regeneration. Inevitably, however, storage in a liquid medium before replantation results in root resorption (11).

Repair with surface root resorption is a more favorable condition for the survival of replanted teeth as the resorbed areas are repaired by newly formed cementum, which does not compromise the root integrity (1). In the present study using an immediate tooth replantation protocol, surface root resorption was identified in all but one of the specimens in the three groups. Histologically, it was characterized by resorption lacunas repaired or being repaired by newly formed cementum along the root surface as well as by the presence of all cellular elements of the PDL, namely cementoblasts, Epithelial rests of Malassez, fibroblasts, Sharpey's fibers, and osteoblasts. Another condition that was favorable to this type of repair was the control of bacterial infection on the periradicular region and external root surface by endodontic treatment and antibiotic therapy (1, 6) because surface resorption can progress to inflammatory root resorption if contaminated dentin tubules are exposed (1, 12).

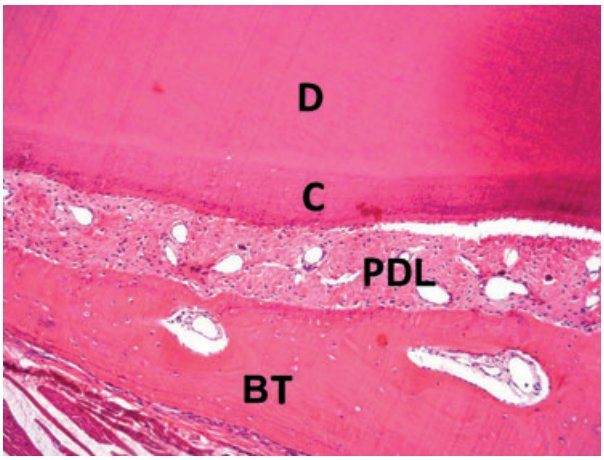

Fig. 1. Group I (control – root canal filling before extraction). Periodontal ligament (PDL) fibers arranged perpendicular to the root surface and attached along the entire extension of the alveolar bone (B) and cementum (C). HE, original magnification ×100. D, dentin.

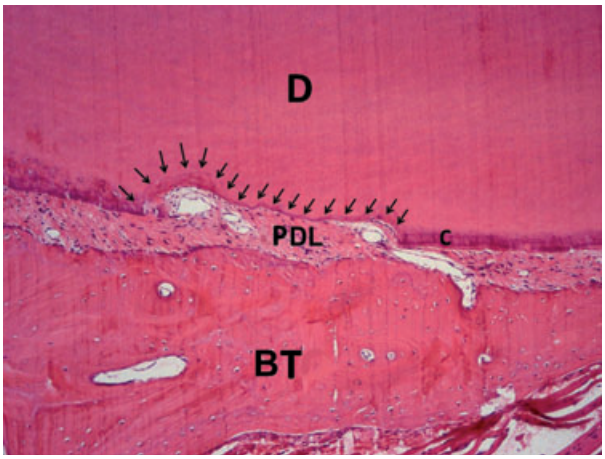

Fig. 3. Group II (root canal filling 1 month after replantation). Root resorption with the deposition of newly formed cementum (arrow). HE, original magnification ×100. PDL, periodontal ligament; C, cementum; D, dentin; BT, bone tissue.

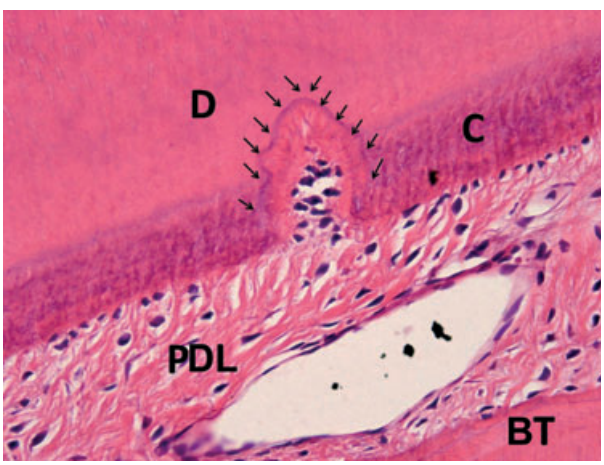

Fig. 2. Group I (control – root canal filling before extraction). Area of root resorption repaired by newly formed cementum (arrow). HE, original magnification ×400. PDL, periodontal ligament; C, cementum; D, dentin; BT, bone tissue.

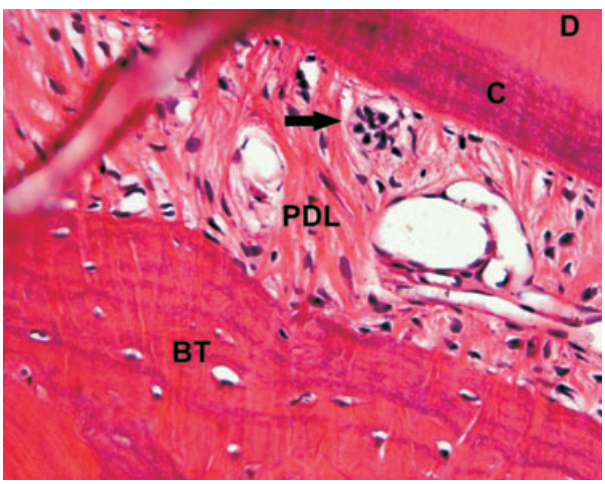

Fig. 4. Group II (root canal filling 1 month after replantation). Presence of Epithelial rests of Malassez (arrow). HE, original magnification ×400. PDL, periodontal ligament; C, cementum; D, dentin; BT, bone tissue.

CH intracanal dressing is still considered as the best medication for replanted teeth (13–16). In spite of its excellent biological properties, however, CH has some disadvantages such as long treatment duration (17, 18), need of successive changes of the medication (17, 18), and weakening of the root structure after prolonged intracanal therapy (19–21).

It has been claimed that definitive root canal filling can be performed after 1 month of CH therapy if endodontic treatment is initiated between 7 and 14 days after replantation at which time the pulp tissue, although necrotic because of rupture of the neurovascular bundle, is not yet thoroughly contaminated (22). In this case, the effect of CH would be to alkalinize the dentin, creating favorable conditions for the action of alkaline phosphatase, which is an important enzyme in mineralized tissue formation, while creating unfavorable conditions for the activity of osteoclastic acid hydrolase (15). However, it has been demonstrated that the CH action is maintained by the alkalinization of the medium and that the high pH achieved with the use of a CH-based intracanal dressing can decrease depending on the sealer used for definitive canal obturation (23). Previous studies (23, 25) have shown a decrease in dentin pH in teeth medicated with CH and obturated with zinc oxide and eugenol cement. On the other hand, because of their solubility, CH-based sealers, such as Sealapex®, release calcium and hydroxyl ions in a slower but constant manner, maintaining the high pH promoted by the intracanal dressing (23, 25). The reparative action of CH is an important property for cases of dental trauma because root resorptions are frequent complications after tooth replantation because of the damage to the PDL (15).

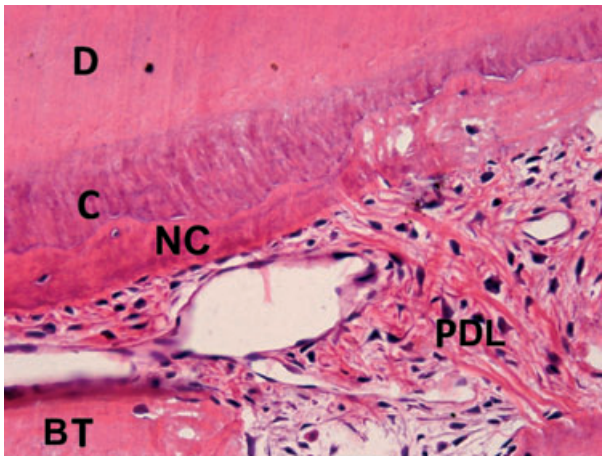

Fig. 5. Group III (root canal filling 6 months after replantation) – area of root resorption repaired by newly formed cementum (NC). HE, original magnification ×400. PDL, periodontal ligament; C, cementum; D, dentin; BT, bone tissue.

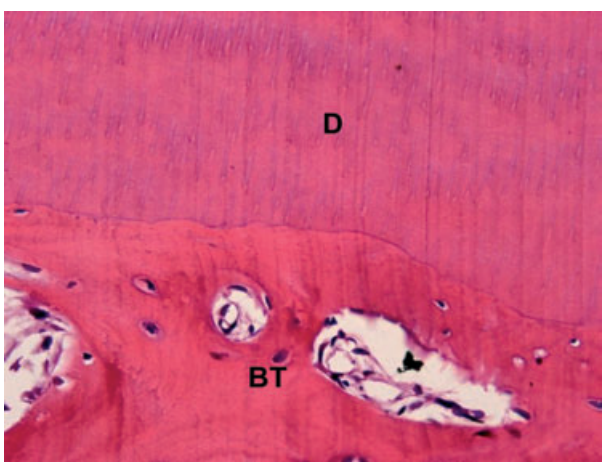

Fig. 6. Group III (root canal filling 6 months after replantation) – presence of replacement resorption in a small area of root surface. HE, original magnification ×100. D, dentin; BT, bone tissue.

The superiority of Sealapex® over zinc oxide and eugenol-based cements has been extensively demonstrated (25–27) and its biological properties, such as biocompatibility, antimicrobial action, and stimulation of mineralized tissue deposition, are well known (25–27). Even its solubility, which was considered as a negative point (28), has been considered as favorable to the deposition of new apical cementum as the constant release of calcium ions maintains a high pH in this region (25, 27). The results of Group I, which was obturated with Sealapex® without previous CH intracanal dressing, were similar to those of the other groups, demonstrating the efficacy of the sealer and its indication for obturation replanted teeth (27).

The results of this study showed that when the viability of PDL cells is preserved on tooth replantation and endodontic treatment is initiated within 10 days after replantation, there is no need of prolonging the CH therapy and the definitive root canal filling can be performed within a shorter time. The advantages of reducing the duration of CH before root canal obturation include prevention of marginal leakage and root fractures, as prolonged intracanal therapy can weaken the root structure; reduction in treatment duration and costs; no need of successive changes of intracanal dressing. The use of CH sealer may contribute positively to the repair of replanted teeth (27) because of its recognized biological properties.

Conclusion

Under the conditions evaluated in this study, the histomorphometric analysis of the repair process suggests that when endodontic treatment is initiated 10 days after immediate tooth replantation, and an antibiotic regimen is associated, definitive root canal filling can be performed after a short-term CH intracanal therapy.

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