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Evaluation of the anti-resorptive ability of an experimental acetazolamide paste for the treatment of late replanted teeth: a study in rats

Graziela Garrido Mori[1,2], Wilson Roberto Poi[1], Lithiene Ribeiro Castilho[1]

[1]Integrated Clinic at Araçatuba Dental School, Unesp, Brazil; [2]Graduation Course of Dentistry at FAI

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Correspondence to: Profa. Dra. Graziela Garrido Mori, Departamento de Cirurgia e Clínica Integrada, Faculdade de Odontologia de Araçatuba, Unesp. Rua José Bonifácio 1193 – CEP – 16015-050 – Araçatuba, SP, Brazil
Tel.: +55 18 3636 3240
Fax: +55 18 3636 3332
e-mail: grazielagm@hotmail.com

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Abstract – When late replantation is performed, the root surface and root canal should be treated. Notwithstanding failures still occur, because of the high rates of root resorption, evidencing the need to search for substances that may inhibit root resorption. The acetazolamide is a known anti-resorptive agent, and its use as root canal dressing may increase the success rates in the treatment of root resorption. Therefore, this study evaluated the effect of an acetazolamide paste used as root canal dressing in late replanted teeth. The study was conducted on 24 maxillary right incisors of rats, which were avulsed and divided in two groups. In group I, the teeth were kept dry for 30 min, had their root surfaces rubbed with a blade, and were treated with 2% sodium fluoride at pH 5.5 for 20 min; the root canals were instrumented and filled with acetazolamide paste; and then the teeth were replanted. In group II, the treatment was similar to group I, except for the root canal dressing, with utilization of calcium hydroxide in group II. At 15 and 60 days after replantation, the animals were killed and the specimens were processed in a histotechnical laboratory for microscopic and morphometric analysis. The results demonstrated the ability of both intracanal substances to limit root resorption, yet they were unable to completely inhibit the root resorption. Replacement resorption lacunae were present in greater proportion in group II, at 60 days. It was concluded that the acetazolamide paste was effective to limit the root resorption, being more effective in limiting the replacement resorption compared with calcium hydroxide.

Tooth avulsion, characterized by complete tooth displacement from the socket, accounts for nearly 0.5–16% of dental traumas (1). In tooth avulsion, several tissues may be involved or damaged, including the periodontal ligament, alveolar bone, gingiva, lips, and dental pulp (1). The periodontal ligament is ruptured, disorganizing its orientation and impairing its viability (1–3). The blood vessel that nourishes the dental pulp is also ruptured, leading to necrosis in most cases (1). These aspects characterize the tooth avulsion as a complex traumatic lesion with difficult prognosis (3).

After avulsion, the tooth should be replaced in the socket attempting to establish its normality. Maintenance of the vitality of cells present on the root is mandatory for a successful replantation (1, 2, 4). Thus, the immediate replantation (1, 5, 6) or storage of the avulsed tooth in a compatible medium for the survival of cells before replantation (1, 5) is fundamental.

Studies conducted in different countries evidence the lack of information of the population on how to manage avulsed teeth (7–10). Thus, instead of performing immediate replantation or maintaining the tooth in adequate media (11), most of the population leave the avulsed tooth exposed to a dry environment, wrapped in plastics and papers, or place it in solutions that are incompatible with the survival of cells present on the root surface. This may lead to ankylosis and root resorption, which are undesirable consequences of tooth replantation (1, 3).

Therefore, to prevent or limit the root resorption and promote the repair, a tooth submitted to late replantation should receive root surface treatment and endodontic therapy (1, 3). Currently, treatment of the root surface is performed by mechanical removal of necrotic rests present on the root surface (12). Fluoride is then applied, because it strengthens the tooth structure by forming fluorapatite and is toxic to hard tissue-resorbing cells (3, 13). Calcium hydroxide is the root canal dressing of choice (1, 13–16) because of its antimicrobial and anti-resorptive characteristics.

Despite these treatments, the failure rates are still high and teeth are ultimately lost in an average period of 4–6 years (17). Therefore, the search for new substances that may inhibit or delay the effects of root resorption and promote the repair is fundamental.

The acetazolamide is a potent inhibitor of carbonic anhydrase (18–20), which is an enzyme frequently found in clast cells (18–20). The carbonic anhydrase catalyzes the reaction between carbonic anhydrase and water, leading to the formation of hydrogen ions (1, 21, 22). These ions are responsible for the low pH in Howship or resorption lacunae (17, 21, 22). The acidic pH promotes the release and action of other enzymes that participate in the resorption process (22). Therefore, with the inhibition of carbonic anhydrase, there will be no reduction in pH and consequently no resorption. Several studies confirm the efficacy of acetazolamide in inhibiting the bone resorption (18–20, 23).

Mori et al. (3), in 2006, observed that acetazolamide solution in a concentration of 10^{-5} M has the ability to inhibit the root resorption in late replanted teeth. The acetazolamide solution was more effective compared with calcium hydroxide. However, because the acetazolamide solution is liquid, the introduction and permanence of this solution in the root canals are impaired. Therefore, the development of an experimental acetazolamide paste would enhance its utilization as a root canal dressing in teeth susceptible to root resorption.

Mori et al. (24) analyzed the biocompatibility of experimental acetazolamide pastes. The results revealed that the experimental paste composed of acetazolamide and saline was biocompatible with the tissues. Thus, the authors suggested that the paste should be tested in teeth susceptible to resorption to check its indication as a root canal dressing.

Within this context, this study evaluated the effect of an experimental acetazolamide paste used as root canal dressing in late replanted rat teeth.

Material and methods

This study was conducted on 24 male rats (Rattus, norvegicus, albinus, Wistar) weighing 250–300 g (approved by the Institutional Review Board for Animal Experimentation of FOA, UNESP – Protocol n. 2008/001852). The animals were kept in cages identified according to the group and experimental period, which were cleaned daily. Before and during the study, the animals were fed with ground chow, except for the first 12 pre- and post-operative hours, and water *ad libitum*.

Surgical intervention

For the surgical interventions, the animals were anesthetized with a combination of ketamine hydrochloride (Dopalen – Sespo Indústria e Comércio Ldta, Jacareí, SP, Brazil) and xylazine hydrochloride (Anasedan – Agribrands do Brasil Ldta, Jacareí, SP, Brazil) by intramuscular injection, at a dose of 0.05 ml per 100 g of animal weight for each drug. Anesthesia was applied with a disposable insulin syringe, followed by antisepsis of the anterior maxillary region with Periogard (Colgate-Palmolive Company, São Paulo, SP, Brazil).

Following, with the aid of surgical instruments, syndesmotomy, luxation and extraction of the maxillary right incisor of each animal were performed, simulating the tooth avulsion.

After tooth extraction, each animal was identified for later replantation of teeth in their respective sockets.

The teeth were then divided in two groups:

1. Group I – the extracted teeth were exposed to dry environment, held by their crowns in pink wax for 30 min, simulating the conditions in which most teeth reach the dental office. After this time, the dental papillae of teeth were removed with a blade n. 11 (Embramac Exportação e Importação, Ribeirão Preto, SP, Brazil). Removal of the dental papilla exposes the root canal and prevents the continuous growth of the tooth after replantation. Then, the dental pulp was removed through the apex using slightly bent Flexofile instruments n. 15 (Dentsply–Maillfer, Ballaigues, Switzerland). Root canal cleaning was completed using Flexofile instruments n. 20 and 25. Root canal irrigation was performed with 1% sodium hypochlorite (Probem Produtos Farmacêuticos e Odontológicos, Catanduva, SP, Brazil) using a Luer Lock syringe with canula 30×4. Then, the periodontal fibers and necrotic cells remaining on the root were removed with a blade n. 15 (Embramac Exportação e Importação, Ribeirão Preto, SP, Brazil) and the teeth were rinsed with saline (Darrow Laboratórios S.A., Rio de Janeiro, RJ, Brazil) and placed in a flask containing 20 ml of 2% sodium hypochlorite at pH 5.5 (Aphoticário, Araçatuba, SP, Brazil) for 20 min. After completion of root surface treatment, the root canals were irrigated with saline, dried with sterile paper points (Tanariman Industrial Ltda, Manacapuru, AM, Brazil), and filled with an experimental acetazolamide paste (Deg Produtos Químicos Ltda, CAS 59- 66-5, São Paulo, SP, Brazil). The apex was not sealed after placement of the dressing because the consistency of the paste allowed its permanence in the root canal. The sockets were then irrigated with saline, and the teeth were replanted in their sockets using curve hemostatic tweezers.
2. Group II – the procedures in this group were similar to group I, except for the root canal dressing, which consisted of a calcium hydroxide paste (CALLEN, S.S. White Artigos Dentários LTDA, Rio de Janeiro, RJ, Brazil).

No retainers were placed after replantation (3). All animals received a single dose of 20,000 U.I. of penicillin G benzathine (Eurofarma Laboratórios Ltda, Itapevi, SP, Brazil) by intramuscular injection.

Achievement of specimens and histotechnical processing

At 15 and 60 days after replantation, six animals in each group were killed by an excessive anesthetic dose. The maxillae were dissected, and the right and left maxillae were separated at the midline, using a blade n. 15. A section made with straight scissors at the region of the third molar allowed achievement of the hemimaxilla containing the replanted tooth.

The specimens were fixated in 10% neutral formalin (Labsynth, Diadema, SP, Brazil) for 7 days. Thereafter, the specimens were rinsed for 24 h in tap water and demineralized in 4.13% EDTA solution (Titriplex III – Merck (108418), São Paulo, SP, Brazil) at pH 7. This

solution was changed weekly until a thin needle could be introduced without resistance. The specimens were macroscopically analyzed to guide the achievement of sections in transverse direction (cervical, medium, and apical thirds).

The specimens were submitted to histotechnical preparation and embedded in paraffin. Sections with 5 μm thickness were obtained at every 50 μm in a microtome, adding up to 20 sections per specimen. These sections were stained with hematoxylin and eosin for light microscopy analysis.

Microscopic analysis

The histological sections were microscopically analyzed observing the following aspects: integrity of tooth structure, presence of cementum on the root surface, tooth ankylosis, occurrence of inflammatory or replacement resorption and characteristics of the connective tissue formed in the periodontal space.

Morphometric analysis

This analysis was performed on the software ImageJ 1.44o (Wayne Rasband, National Institutes of Health, Bethesda, Maryland, USA), used for measurements of areas and perimeters. Fifteen histological sections of each experimental period were obtained using a photo camera (Canon, Tokyo, Japan) connected to a light microscope (Leica Microsystems, Wetzlar, Germany) and to the computer. The images were stored as figures (JPEG) for reading on the software ImageJ.

This software allowed measurement of the perimeter of regions with tooth ankylosis, with fibrous connective tissue perpendicular or parallel to the root, establishing percentages for their occurrence. The quantity of missing cementum on the root surface was calculated. The areas of inflammatory or replacement resorption were also determined.

Statistical analysis

Data were organized in tables and statistically analyzed by the Student *t* test, at a significance level of 5%.

Results

Group I – Acetazolamide paste

Analysis of histological sections at 15 days evidenced the formation of a dense connective tissue with collagen fibers parallel to the root in 73.35% of cases (Fig. 1). In some specimens, the connective tissue contained inflammatory cells, especially neutrophils. In only 5.10% of specimens, the dense connective tissue exhibited collagen fibers perpendicular to the root, similar to the periodontal ligament. Tooth ankylosis, characterized by the junction of bone tissue and the tooth surface, was present in 11.32% of specimens at 15 days.

At 60 days, there was a decrease in connective tissue similar to the periodontal ligament, affecting only 1.21% of sections analyzed. There was also a mild reduction in the quantity of connective tissue parallel to the root surface. Tooth ankylosis had a mild increase, affecting 18.55% at 60 days (Fig. 2). There was no statistically

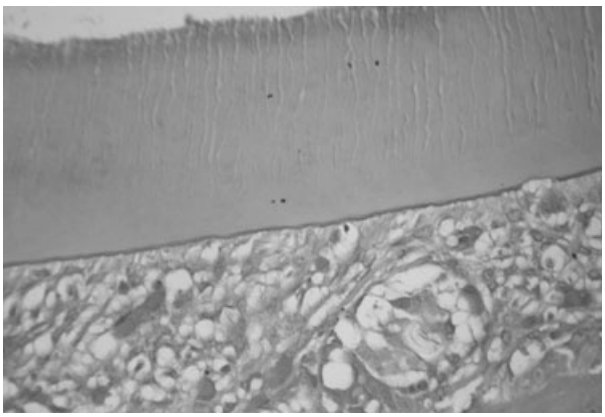

Fig. 1. Group I (acetazolamide paste), 15 days: integrity of root structure, presence of cementum in root surface and dense connective tissue with collagen fibers parallel to the root. Original magnification 40×.

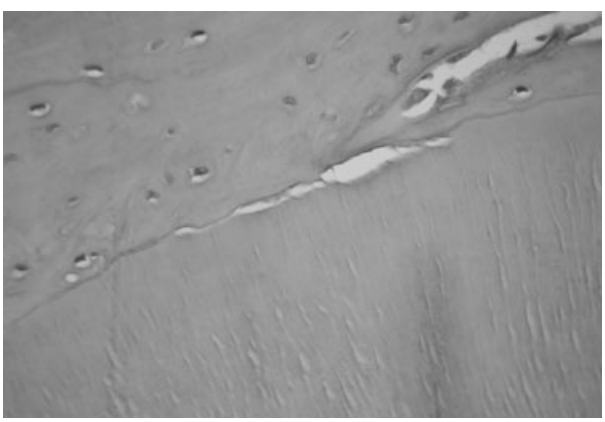

Fig. 2. Group I (acetazolamide paste), 60 days: integrity of root structure, presence of cementum in root surface and tooth ankylosis. Original magnification 40×.

Table 1. Mean values of percentages of histological events according to the experimental period in group I

	Experimental period (%)	
Histological event	15 days	60 days
Inflammatory resorption	0.76	2.27
Replacement resorption	0.01	0.36
Lack of cementum on the root	10.23	12.83
Tooth ankylosis	11.32	18.55
Connective tissue parallel to the root	73.35	67.41
Connective tissue perpendicular to the root	5.10	1.21

[a]With statistically significant difference from [b]($P < 0.05$).

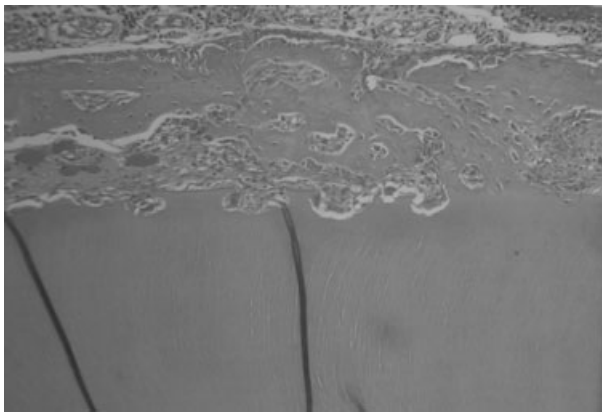

Fig. 3. Group I (acetazolamide paste), 15 days: presence of dense connective tissue with collagen fibers parallel to the root, toot ankylosis and small lacunae of inflammatory resorption. Original magnification 40×.

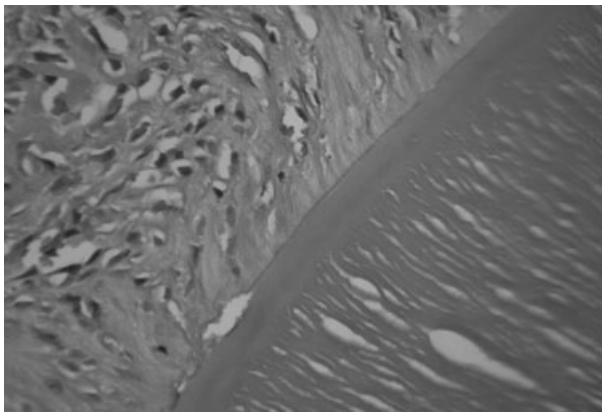

Fig. 5. Group II (calcium hydroxide paste), 15 days: integrity of root structure, presence of cementum in root surface and dense connective tissue with collagen fibers perpendicular to the root. Original magnification 40×.

significant difference between experimental periods of 15 and 60 days in the aforementioned events (Table 1).

Analysis of the root surface evidenced the presence of cementum in most specimens analyzed in both experimental periods (Table 1) (Figs 1 and 2). Consequently, a low percentage of root resorption was found in this group. The inflammatory resorption lacunae accounted for 0.76% and 2.27% at 15 and 60 days, respectively (Figs 3 and 4). The low occurrence of replacement resorption was also observed in this group (Fig. 4) (Table 1). There was no statistically significant difference between experimental periods in the aforementioned events.

Group II – Calcium hydroxide paste

At 15 days, there was dense connective tissue with collagen fibers perpendicular to the root in 37.79% of specimens (Fig. 5). The dense connective tissue parallel to the root was present in 50.48% of specimens. Tooth ankylosis accounted for only 6.51% of cases at 15 days.

At 60 days, there was an increase in the occurrence of tooth ankylosis (Fig. 6) and dense connective tissue parallel to the root, yet without statistically significant difference compared with 15 days (Table 2). However, the presence of connective tissue similar to periodontal

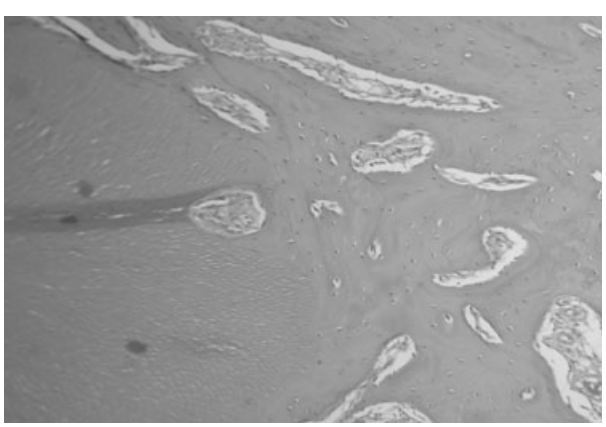

Fig. 4. Group I (acetazolamide paste), 60 days: presence of tooth ankylosis and lacunae of root resorption.

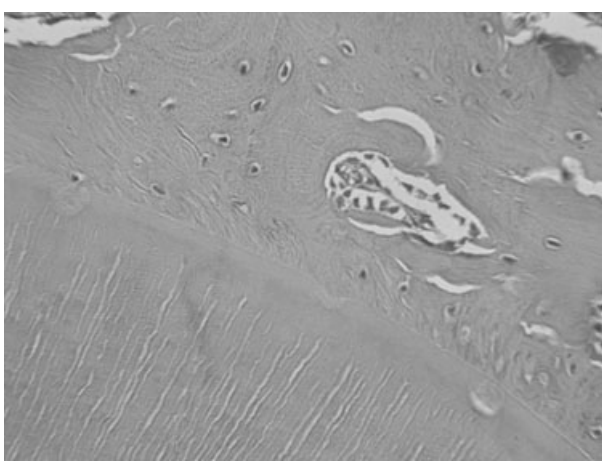

Fig. 6. Group II (calcium hydroxide paste), 60 days: tooth ankylosis, presence of cementum in root surface and replacement resorption lacunae. Original magnification 40×.

Table 2. Mean values of percentages of histological events according to the experimental period in group II

	Experimental period (%)	
Histological event	15 days	15 days
Inflammatory resorption	0.47[a]	2.06[b]
Replacement resorption	0.06[a]	1.93[b]
Lack of cementum on the root	5.22[a]	27.27[b]
Tooth ankylosis	6.51	19.53
Connective tissue parallel to the root	50.48	52.04
Connective tissue perpendicular to the root	37.79[a]	1.16[b]

[a]With statistically significant difference from [b]($P < 0.05$).

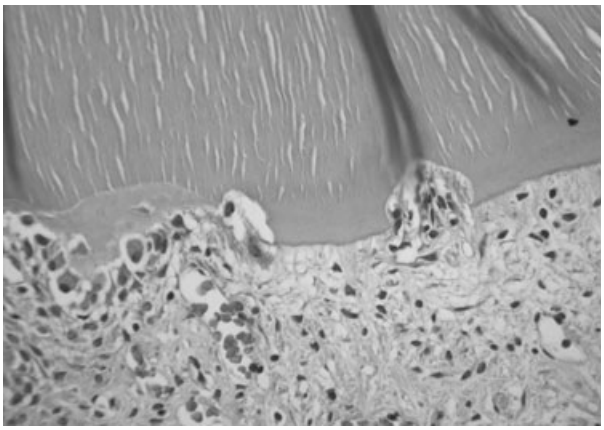

Fig. 7. Group II (calcium hydroxide paste), 15 days: presence of dense connective tissue with collagen fibers parallel to the root and root resorption lacunae. Original magnification 40×.

ligament was significantly reduced at 60 days ($P < 0.05$) (Table 2).

Analysis of the root surface evidenced the absence of cementum on the root surface in only 5.22% of cases at 15 days (Fig. 5). The percentage of cementum on the root was significantly reduced at 60 days, because the cementum was absent in 27.27% of cases ($P < 0.05$) (Table 2).

At 15 days, few root resorption lacunae were observed (Fig. 7) (Table 2). At 60 days, the percentage of inflammatory and replacement resorption lacunae was increased in this group ($P < 0.05$) (Table 2) (Figs 6 and 8).

Comparison between experimental groups

Comparison of the results obtained in groups I and II revealed the similar occurrence of tooth ankylosis (Table 3). The dense connective tissue with collagen fibers parallel to the root was significantly greater in group I compared with group II, at 15 days ($P < 0.05$). However, there was no difference between groups at 60 days. The connective tissue perpendicular to the root surface, similar to the periodontal ligament, was more significant at 15 days in group II (Table 3).

Great quantity of cementum was present on the root surface in both groups at 15 days and in group I at 60 days. There was significant reduction in the percentage of cementum on the root in group II at 60 days ($P < 0.05$) (Table 3).

Small percentages of inflammatory resorption were observed in both groups. However, there was statistically significant difference in the occurrence of this resorption in group I at 15 days and in group II at 60 days ($P < 0.05$) (Table 3). Low occurrence of replacement resorption lacunae was observed in group I in both experimental periods and in group II at 15 days. Comparison of data of replacement resorption with group II at 60 days revealed its significant increase ($P < 0.05$) (Table 3).

Discussion

This study used rats as experimental model. The initial use of rats to test hypotheses and indicate ways for research in other animals and in humans is justified because they are easy to achieve and maintain, and the results found in these animals are similar to those observed in dogs and monkeys (3, 25–28).

The tooth selected for the study was the maxillary incisor. This tooth presents some peculiarities: it is a tooth with continuous growth and curved root and presents enamel on the entire buccal surface extent (28). Thus, for the use of these teeth, these differences are

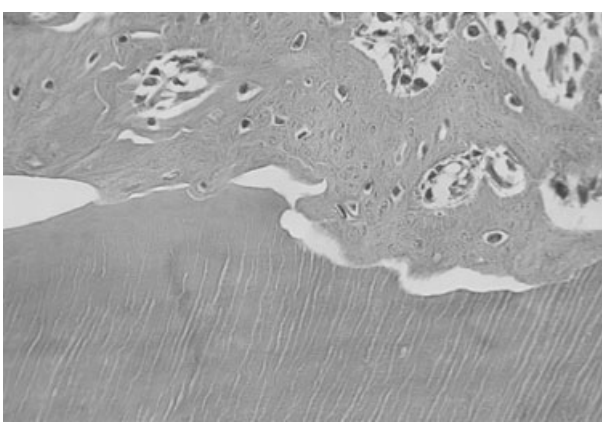

Fig. 8. Group II (calcium hydroxide paste), 60 days: presence of tooth ankylosis and replacement resorption lacunae. Original magnification 40×.

Table 3. Mean values of percentages of histological events according to the experimental period in groups I and II

	Experimental period (%)			
	Group I		Group II	
Histological event	15 days	60 days	15 days	60 days
Inflammatory resorption	0.76[a]	2.27	0.47[a]	2.06[b]
Replacement resorption	0.01[a]	0.36[a]	0.06[a]	1.93[b]
Lack of cementum on the root	10.23[a]	12.83[a]	5.22[a]	27.27[b]
Tooth ankylosis	11.32	18.55	6.51	19.53
Connective tissue parallel to the root	73.35[a]	67.41	50.48[b]	52.04
Connective tissue perpendicular to the root	5.10[a]	1.21[a]	37.79[b]	1.16[a]

[a]With statistically significant difference from [b]($P < 0.05$).

compensated as follows (28): the dental papillae present in the apical region of these teeth, which is responsible for its continuous growth, was removed during the experiment; the curved root facilitated the permanence of the tooth in its socket after tooth replantation; and the buccal surface was eliminated during analysis of histological sections, because the morphology of proximal and lingual aspects of these teeth resembles those of human beings.

The incisors of rats are delicate teeth and thus must be extracted with care and caution. The teeth were extracted in an average time of 2 min. If fractures were detected, either in the tooth or in the sockets, the animal was excluded from the study. Tooth fracture occurred in two animals and in the socket of one animal, which were thus replaced.

The morphology of this tooth also studied for its selection for accomplishment of root canal treatment before tooth replantation. Conventional coronal opening was not possible because of the small diameter of the lingual aspect. Retrograde instrumentation and placement of intracanal dressing may be performed because the tooth present open apex (26, 28). All specimens were instrumented with Flexofile instruments n. 15, 20, and 25 throughout the root canal extent. The complete removal of pulp tissue was confirmed by the absence of bleeding and tissue in instruments and paper points used during the root canal therapy. The curved root canal can be submitted to retrograde instrumented and placement of intracanal dressing. According to some authors, root canal treatment must be carried out in the hand, before accomplishment of dental replantation (1, 3, 11–13, 26, 28, 29).

Cross-sectional cuts in the cervical, medium, and apical thirds were made in the specimens. These cuts allowed evaluation of the largest root extent as possible. The integrity of tooth structure, presence of cementum on the root surface, tooth ankylosis, occurrence of inflammatory or replacement resorption, and characteristics of the connective tissue formed in the periodontal space were observed and measured. This method was used in previously published works (3, 28, 29).

The presence of connective tissue similar to periodontal ligament was small in both experimental groups at 60 days. Despite the higher levels at 15 days in group II, this tissue was replaced with time. In group II, there was replacement of this tissue by areas of tooth ankylosis, connective tissue parallel to the root and root resorption. The greater quantity of connective tissue similar to periodontal ligament may be explained by the arrangement of remaining alveolar periodontal ligament fibers on tooth replantation. However, owing to the absence of specific cells, the tissue was replaced by the reported histological events (3, 29).

Analysis of the root surface revealed significant reduction in cementum on the root in group II at 60 days (Table 3). This demonstrates that calcium hydroxide loses its action with time, because the absence of cementum resorption was small at 15 days in this group. The small loss of cementum in group I demonstrates the anti-resorptive ability of acetazolamide (3, 18–20, 23). A direct relationship between the presence of cementum on the root surface and root resorption lacunae may be established, because greater areas of denuded surface and root resorption were observed in the same group and experimental periods.

Though present, the occurrence of root resorption was relatively low in the experimental groups in this study. This emphasized the action of acetazolamide (3, 18–20, 23) and calcium hydroxide (1, 13–16) in limiting the resorption process. A mild superiority of the acetazolamide paste in limiting the replacement resorption was observed. When the calcium hydroxide paste was used, the replacement resorption lacunae were more significant ($P < 0.05$) (Table 3). Even though both substances influenced acidification of the area to avoid the resorption process, the acetazolamide is more long lasting.

A study conducted by Mori et al. (3) evidenced the superiority of acetazolamide compared with calcium hydroxide to limit the root resorption. In this study, the authors used an acetazolamide solution and no root resorption lacunae were observed at 60 days. When the acetazolamide paste was used, a small occurrence of root resorption was observed. This may be explained by the composition of the paste and its consequent capacity of diffusion through the dentinal tubules and tissues, limiting its action compared with the acetazolamide solution.

Current research demonstrated that local steroids used in intracanal medication might have a positive effect on impairing, preventing, and delaying root resorption (30–32). The steroids were more efficient that calcium hydroxide (32) or gutta-percha (30), because more favorable healing and small rates of root resorption were observed when the steroids were used. Chen et al. (31) reported that steroids can be used in the root canal space to prevent the root resorption, especially the inflammatory resorption.

Small rates of root resorption had been also observed in the experimental group (acetazolamide paste) in this study. This can suggest the effectiveness of the experimental paste in preventing root resorption similarly to local steroids, studied currently. To our knowledge, no study so far has directly analyzed these steroids to acetazolamide, but the results of these drugs can be compared and indicate the favorable effects of steroids and acetazolamide in the treatment of tooth reimplantation.

Further studies should be conducted to analyze the ability of acetazolamide paste for the prevention and treatment of root resorption comparing with intracanal medication: acetazolamide solution (3), local steroids (30–32) and calcium hydroxide paste (1, 13–16).

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