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Intracanal bisphosphonate does not inhibit replacement resorption associated with delayed replantation of monkey incisors

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Abstract – Progressive replacement resorption following delayed replantation of avulsed teeth has proved to be an intractable clinical problem. A wide variety of therapeutic approaches have failed to result in the predictable arrest of resorption, with a good long-term prognosis for tooth survival. Bisphosphonates are used in the medical management of a range of bone disorders and topically applied bisphosphonate has been reported to inhibit root resorption in dogs. This study evaluated the effectiveness of a bisphosphonate (etidronate disodium) as an intracanal medicament in the root canals of avulsed monkey teeth, placed before replantation after 1 h of extraoral dry storage. Incisors of six *Macaca fascicularis* monkeys were extracted and stored dry for 1 h. Teeth were then replanted after canal contamination with dental plaque (negative control) or after root canal debridement and placement of etidronate sealed in the canal space. A positive control of calcium hydroxide placed 8–9 days after replantation was also included. All monkeys were sacrificed 8 weeks later and block sections were prepared for histomorphometric assessment of root resorption and periodontal ligament status. Untreated teeth showed the greatest extent of root resorption (46% of the root surface), which was predominantly inflammatory in nature. Calcium hydroxide treated teeth showed the lowest overall level of resorption (<30% of the root surface), while the bisphosphonate-treated group was intermediate (39%). Ankylosis, defined as the extent of the root surface demonstrating direct bony union to both intact and resorbed root surface, was the lowest in the untreated control group (15% of the root surface), intermediate in the calcium hydroxide group (27%) and the highest in the bisphosphonate group (41%). Bony attachment to the tooth root was divided approximately equally between attachment to intact cementum and to previously resorbed dentin. Overall, bisphosphonate resulted in a worse outcome than calcium hydroxide in terms of both root resorption and ankylosis.

The prognosis for avulsed teeth replanted after prolonged extraoral time is generally unfavourable if the tooth is stored dry (1, 2). A reduced prognosis has been reported if the extroral dry time exceeds 5 min (2) and the prognosis is generally regarded as hopeless if the tooth is stored dry for an hour or more. The major reason for the poor prognosis is death of attached periodontal ligament cells leading to progressive resorption of the root. This replacement resorption is characterized by direct bony attachment to the root surface and gradual replacement of dentin by bone as part of normal physiological bone turnover (3, 4). Replacement resorption becomes dominant only after inflammatory resorption (resulting from bacterial infection of the canal space) is controlled by canal debridement and medication (4–6).

Attempts to manage replacement resorption have met with only very limited success, despite an extensive search for suitable agents and techniques (7). Most of the effort has been directed towards topical treatment of the root surface before replantation. In many instances, this has involved adapting procedures from clinical periodontology that are intended to promote periodontal reattachment. The diversity of approaches includes attempts to slow resorption by reducing the solubility of the mineral phase of dentin (e.g. topical fluorides) and the use of cytokines and growth factors to stimulate periodontal regeneration (summarized in Table 1). Systemic administration of antibiotics and anti-inflammatory agents and the use of intracanal medicaments have also been evaluated with at best modest results. The prognosis is markedly improved if teeth are stored moist until replantation, preferably in milk or more specialized storage media that promote survival of periodontal ligament cells (8–10) and public awareness campaigns have emphasized the benefits of this approach. Nevertheless, many avulsed teeth are still subjected to adverse storage conditions and the need remains for an agent that inhibits or arrests replacement resorption.

Table 1. Strategies to inhibit replacement resorption associated with replantation after extended dry time. Some studies have used a combination of agents and procedures. Root filling before or soon after replantation is regarded as a 'negative control' procedure rather than active management, and is not included in the list below

	Species	References
1. Topical application of agent to the root surface		
A. Agents that slow resorption (dissolution of hydroxyapatite)		
Fluorides	Human, monkey, dog, rat	21–29
Bisphosphonates	*In vitro*, dog, rat	13, 14, 30
Gallium nitrate	*In vitro*	30
Polylactic acid	Dog	31
B. Anti-inflammatory agents		
Dexamethasone	Human, rat, dog	32–34
C. Antibiotics	Human, dog, monkey	24, 28, 29, 35–38
D. Agents removing damaged periodontal ligament		
Sodium hypochlorite	Monkey	39, 40
Enzyme solutions	Monkey	40
E. Agents promoting periodontal reattachment		
Demineralizing solutions (citric acid, HCl)	Dog, monkey	41–45
Emdogain®	Human, dog, monkey, rat	46–51
Cytokines and growth factors (FGF, BMP)	Dog, monkey	52, 53
Adhesins (fibronectin)	Monkey, baboon	54, 55
F. Other		
Miscellaneous (ATP, lyophilized autologous plasma)	Rat, monkey	56, 57
Tissue culture	Monkey	58
Surgical resection, replantation	Human	59
Ascorbic acid	Rat	60
2. Systemically administered agents		
Antibiotics	Human, dog	34, 38, 61, 62
Anti-inflammatory agents	Dog	33, 63
3. Intracanal medicaments		
Calcium hydroxide	Human, monkey, dog	5, 6, 64–66
Antibiotic-corticosteroid mixtures (Ledermix®)	Monkey, dog	67, 68
Calcitonin	Monkey	69
Acetazolamide	Rat	15

Bisphosphonates are low molecular weight agents based on bisphosphonic acid (an analogue of pyrophosphate in which two phosphorus atoms are linked by a carbon atom), which act by chemisorption to calcium phosphate surfaces. The stable binding inhibits the formation, growth and dissolution of hydroxyapatite crystals. As a result, both bone formation and bone resorption will be inhibited; depending on the side-chain substitutions of the bisphosphonic acid, selective inhibition of resorption may result. Etidronate disodium (the di-sodium salt of 1-hydroxyethylidene bisphosphonic acid) inhibits both the formation and dissolution of hydroxyapatite crystals and it has been clinically shown to inhibit bone turnover. Accelerated bone turnover (as occurs in Paget's disease) is inhibited to a greater extent than normal bone turnover. On the other hand, alendronate [(4-amino-1-hydroxybutylidene) bisphosphonic acid] inhibits resorption with little effect on bone formation (11, 12).

In previous studies in dogs and rats, soaking the roots of avulsed teeth for 5 or 10 min in a solution of alendronate before replantation inhibited root resorption, but not ankylosis (13, 14). In this study, we investigated the ability of etidronate used as an intracanal medicament to inhibit replacement resorption in monkey incisors. The rationale for using etidronate was that this agent inhibits bone turnover (both formation and resorption) and hence may delay the progressive replacement of dentin by bone. Using the canal space as a reservoir for long-term release of the agent may also prolong its effectiveness relative to a one time topical application to the root surface before replantation. A similar approach using intracanal acetazolamide in rat incisors (15) resulted in inhibition of root resorption and a reduced extent of ankylosis.

Material and methods

Bisphosphonate preparation

Tablets of etidronate disodium (200 mg Didronel®, Procter and Gamble Pharmaceuticals, Cincinnati, OH, USA) were crushed and added to normal saline to produce thick slurry, immediately before insertion into the canals. The preparation thus consisted of a saturated solution with a large excess of undissolved material.

Experimental animals

Six mature *Macaca fascicularis* monkeys (3–5 years old) of both genders were housed in the primate colony of the University of Malaya and fed a standard pellet and fruit diet. Radiographs were taken to ensure that the incisors had fully formed apices. General anaesthesia was achieved by intramuscular injection of 4–6 mg kg^{-1} of tiletamine-zolazepam (Zoletil®, Virbac Laboratories, Carros, France). Animals were fed a soft fruit diet for 1 day following the avulsion/replantation procedure.

The study was granted approval by the Ethics in Animal Experimentation Committee of the University of Malaya.

Avulsion and replantation

A self-curing acrylic resin template was constructed of the incisor region of the maxilla and mandible, to aid in realignment of replanted teeth to their original positions. Four maxillary and two mandibular incisors were then extracted using elevators and extraction forceps and stored dry in Petri dishes for 60 min. Depending on the experimental group, canals were then either infected with bacteria or prepared and medicated (see below), while the teeth were held in gauze soaked in sterile saline. Working length was based on tooth length measurements obtained after extraction. The teeth were then replanted in their sockets after a total of 75 min extraoral time using gentle pressure and the final position was checked with the template for correct repositioning. Teeth were not splinted after replantation (16).

Endodontic procedures and canal medication

For the negative control group and for teeth subsequently medicated with calcium hydroxide, endodontic access was obtained 60 min after avulsion via a labial approach using a high speed bur with water cooling (17). The pulp was then disrupted using a file inserted into the canal and contaminated with dental plaque obtained from the same animal, by repeated insertion of a contaminated file. The access was sealed with zinc oxide-eugenol cement (IRM, Caulk Dentsply, Milford, DE, USA).

For the bisphosphonate-treated group, canals were medicated before replantation. After 60 min of dry storage, access was gained as above and canals were prepared using ProFile rotary nickel–titanium instruments (ProFile®, Dentsply Maillefer, Baillagues Switzerland) to size 35/0.04 taper, 1 mm short of the anatomic apex. Sodium hypochlorite 2.6% was used as the standard irrigant, with care taken not to allow the irrigant to contact the external root surface. The canal was then flushed with 2.5 ml EDTA (EDTA Solution, 17%™, Pulpdent Corp., Watertown, MA, USA) for 3 min, followed by a final sodium hypochlorite rinse. The canals were then dried with paper points and filled with thick slurry of bisphosphonate suspended in saline, using a lentulo spiral. The access opening was restored with IRM.

With the calcium hydroxide treated group, canals were debrided and medicated 8–9 days after replantation. Under general anaesthesia, incisors were isolated with rubber dam and the crowns were disinfected with 70% ethanol. The temporary restoration was removed and canals were prepared using ProFile rotary nickel–titanium instruments (ProFile®, Dentsply Maillefer) to size 30/0.04 taper, as described above. The canal was dried and filled with a non-setting calcium hydroxide paste (Pulpdent Paste®, Pulpdent Corp.) using a lentulo spiral, and sealed with IRM.

Tissue processing and histomorphometry

Monkeys were sacrificed 8 weeks after avulsion and replantation, by intravenous injection of pentobarbitone sodium (Sagatal®, Rhone Merieux, Ireland). Tissues were perfused with 10% neutral buffered formalin via intracardiac cannulation and block specimens containing the required teeth were removed, fixed in formalin for an additional 2 weeks and decalcified in 10% EDTA solution at pH 6.9. Routine block sections containing the roots of all four incisors were prepared for histological examination. Three consecutive 5 μm sections were cut perpendicular to the long axis of the teeth at 500 μm intervals from the root apex to the approximal alveolar crest and stained with H&E (17–19).

One of the three sections at each level was selected for morphometric evaluation and examined using a Nikon Eclipse E400 microscope equipped with an Evolution MP camera connected to a computer with image capture software (Image-Pro Express, Media Cybernetics, Inc., Silver Spring, MD, USA). A circular grid with eight equiangular registration points was superimposed on the image, with the first registration point oriented to the mid-buccal surface of the root (17). The root surface and adjacent periodontal ligament were scored at each registration point by two examiners who were blinded with regard to the treatment group. The classification systems used to describe the root surface and the periodontal ligament are given in Table 2.

Data analysis

The total number of registration points averaged approximately 80 per tooth, representing 10 levels of each root. Each category of root surface and periodontal ligament condition was expressed as a percentage of the total number of registration points for that root. Statistical analysis was performed as one-way ANOVA with *post hoc* tests (Tukeys' test), comparing the frequency of each category of root surface or periodontal ligament condition among the three groups.

Results

Losses and exclusions

Ten teeth were lost within the first week post-replantation, a consequence of not splinting the teeth. Two teeth in separate animals had periapical abscesses and were excluded from the analysis. One tooth showed epithelial downgrowth to the apical one-third of the root and data were recorded only apical to the level of the epithelium.

Resorption and ankylosis

The distribution of the different types of root resorption (surface, inflammatory and replacement) is depicted in Fig. 1, without subdivision into the different categories of active, ceased or healed. The negative control group showed the greatest extent of root resorption (46.8% ± 20.0% of the root surface), most of which was inflammatory resorption (30.0%). Teeth medicated with calcium

Table 2. Categories for scoring the status of the root surface and periodontal ligament status at each registration point

A. Root surface	
Intact	Normal root contour with intact cementum and periodontal ligament.
Surface resorption	Shallow areas of resorption confined to cementum, with healthy adjacent periodontal ligament.
Inflammatory resorption ligament	Resorption involving dentin, and accompanied by inflammatory cells in the adjacent periodontal.
Replacement resorption	Areas showing direct bony union to previously resorbed cementum or dentin, with obliteration of the normal periodontal ligament space.
In addition, the status of the resorptive lesion was categorized as active, ceased or healed. Ankylosis was recorded as attachment to intact cementum or to a previously resorbed surface (either cementum or dentin).	
B. Periodontal ligament	
Normal	Healthy, intact ligament.
Inflamed	Inflammatory cells present in the periodontal ligament space.
Active remodelling	Few inflammatory cells, but osteoclasts or plump young fibroblasts suggestive of active remodelling.
Healing	Root resorption had occurred but the root surface was covered by cementum with periodontal ligament fibers attached.
Bone	Periodontal ligament space obliterated by bone attached to the root surface.
Epithelial downgrowth	Epithelial cells attached to the root surface at a level apical to the normal level of attachment. These sites were excluded from subsequent analysis.

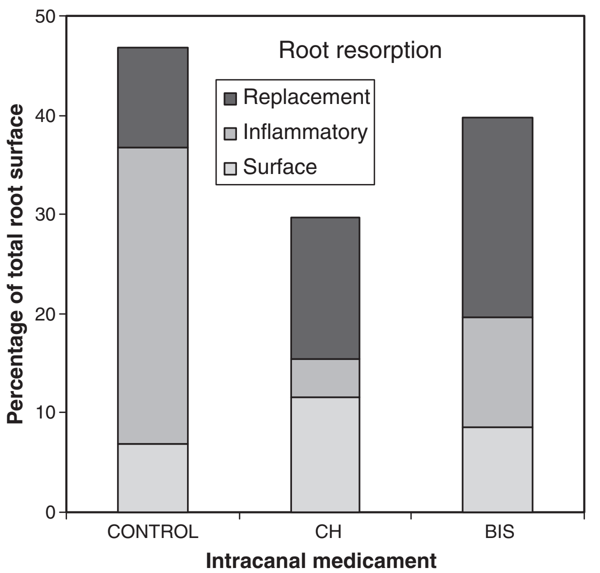

Fig. 1. The effects of calcium hydroxide and bisphosphonate on root resorption. The vertical bars indicate the cumulative extent of surface, inflammatory and replacement resorption as a percentage of the total root surface. CONTROL, negative control (no canal debridement or medication, $n = 5$); CH, calcium hydroxide medication ($n = 7$); BIS, bisphosphonate medication ($n = 11$). Definitions of the different categories of root resorption are given in Table 2.

hydroxide showed the least resorption (29.7% ± 19.6%), with replacement resorption predominating (14.3%) and a low level of inflammatory resorption (3.9%). The bisphosphonate-treated group had an intermediate extent of resorption (39.7% ± 20.6%), but the highest level of replacement resorption (20.1%). Because of large variations among teeth, overall, no significant differences in root resorption were found among the three groups ($P > 0.05$, one-way ANOVA). Inflammatory resorption was significantly greater in the negative control than in the two treatment groups ($P = 0.02$), while replacement resorption was significantly less ($P = 0.04$), but no significant differences were found between calcium hydroxide and bisphosphonate groups.

Ankylosis was defined as direct bony union to intact cementum plus union to previously resorbed cementum or dentin and is shown in Fig. 2. Ankylosis was least in the untreated control group (14.8% ± 11.5%) and greatest in the bisphosphonate-treated group (41.5% ± 17.5%), with statistically significant differences among all groups ($P < 0.05$, one-way ANOVA). No significant difference was found between the calcium hydroxide and bisphosphonate groups, but both were significantly higher ($P = 0.01$) than the untreated control. The distribution between union to intact root surface and union to previously resorbed root surface was approximately equal in all groups. The bisphosphonate-treated group showed the greatest extent of both types of union.

Periodontal ligament status

The different categories of periodontal ligament status are defined in Table 2, and shown for the three groups in Fig. 3. The calcium hydroxide group showed the

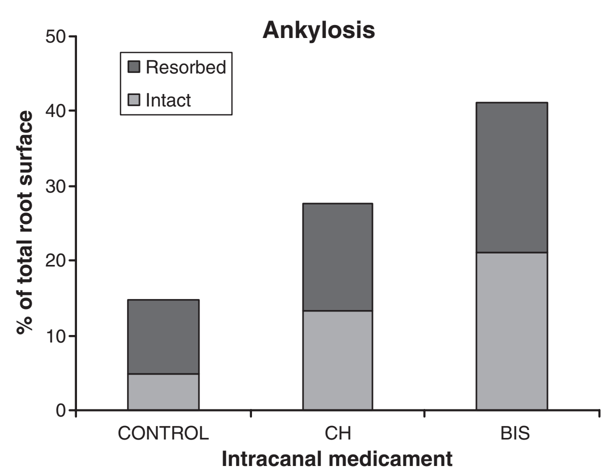

Fig. 2. Extent of ankylosis in the three experimental groups, showing the percentage of the root surface exhibiting direct bony union to intact cementum and to previously resorbed cementum or dentin. Legends and numbers are as in Fig. 1.

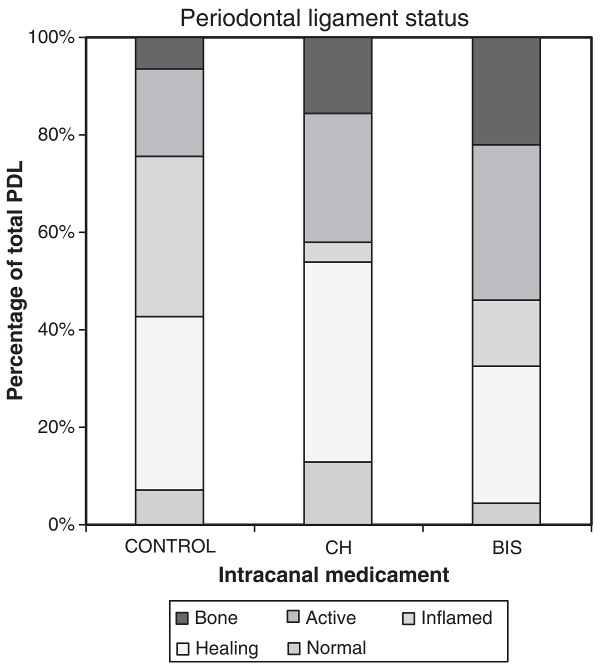

Fig. 3. The periodontal ligament status of untreated teeth compared with those with debrided canals and medication with calcium hydroxide or bisphosphonate. Legends and numbers are as in Fig. 1 and definitions of periodontal ligament status are in Table 2.

numerically (but not significantly) greatest extent of intact plus healing ligament and the bisphosphonate group was the least. Inflamed periodontal ligament was the most frequent in the untreated control group and the least in the calcium hydroxide group. Separate one-way ANOVA with *post hoc* tests between groups for each category of periodontal status indicated that the untreated control showed significantly more inflamed ligament than the calcium hydroxide group ($P = 0.04$) and significantly less bony replacement of the ligament space than both treatment groups (vs calcium hydroxide, $P = 0.05$; vs bisphosphonate, $P = 0.004$). No other statistically significant differences were observed.

Overall outcome

The overall response for each treatment group was defined in the general terms of favourable and unfavourable outcomes. A *favourable response* for the root surface included the categories of normal root surface, surface resorption and healed resorption of outer or inner dentin. An *unfavourable response* for the root surface included the categories of active and ceased resorption (outer and inner dentin and complete resorption) plus direct bony union (Fig. 4) to intact or resorbed cementum and dentin (defined in Table 2). The calcium hydroxide-treated group showed the best numerical outcome, with 38.6% ± 21.0% (mean ± SD) of the total root surface indicating an unfavourable response, compared with 50.8% ± 28.9% for the untreated control group and 60.5% ± 17.6% for the bisphosphonate-treated group. Differences among groups were statistically significant ($P < 0.05$, one-way ANOVA), with the bisphosphonate group significantly worse than calcium hydroxide-treated teeth ($P = 0.029$).

Periodontal response was also categorized as *favourable* (which included normal intact and healing categories) and *unfavourable* (inflamed, active remodelling and bone, as defined in Table 2). Periodontal status showed similar trends to the root surface, but with higher levels of unfavourable response: negative control: 56.6% ± 28.0%; calcium hydroxide: 46.3% ± 29.9%; bisphosphonate: 64.0% ± 21.7%. No significant differences were found among the three treatment groups ($P > 0.05$, one-way ANOVA).

Discussion

Replacement resorption associated with the delayed replantation of avulsed teeth is a progressive condition, resulting in the gradual replacement of normal root structure by bone. Despite great effort involving a wide range of agents and procedures (summarized in Table 1), the best result to date appears to be a slowing of the rate of resorption rather than a definitive arrest (7, 13, 15). The potential advantage of intracanal medication is that a reservoir of the agent, which can be periodically replenished via the access opening, may offer long-term protection against root resorption and replacement by bone. Etidronate is more soluble than calcium hydroxide, and a saturated solution with excess undissolved material potentially serves as an effective long-term source of the material.

The typical pattern of events following delayed replantation of avulsed incisors was seen in the negative (no treatment) and positive (calcium hydroxide) control groups in this study (5, 6, 20). Teeth replanted with an infected canal space without debridement or medication showed substantial inflammatory root resorption, occasionally penetrating through the entire thickness of dentin to the canal space. Inflamed periodontal ligament space was also characteristic of this group. On the other hand, teeth undergoing canal debridement and medication with calcium hydroxide demonstrated less inflammatory resorption and a greater extent of replacement resorption than the negative control group.

The loss of teeth post-replantation reduced sample size (5 controls, 7 calcium hydroxide, 11 etidronate), making it more difficult to demonstrate significant differences among groups. Nonetheless, the etidronate-treated groups showed a significantly worse outcome overall than calcium hydroxide. No beneficial effect of intracanal medication with bisphosphonate was observed. The extent of inflammatory resorption was less than in the negative control group, but higher than in the calcium hydroxide group. Replacement resorption and ankylosis were higher than in the calcium hydroxide group, with ankylosis occurring over more than 40% of the root surface. The lower inflammatory resorption and inflamed periodontal ligament relative to the negative control can be explained by canal debridement before replantation, resulting in removal of bacteria and pulp tissue debris. Hence, the inflammatory stimulus was less than in the untreated control. There is no reason to believe that the

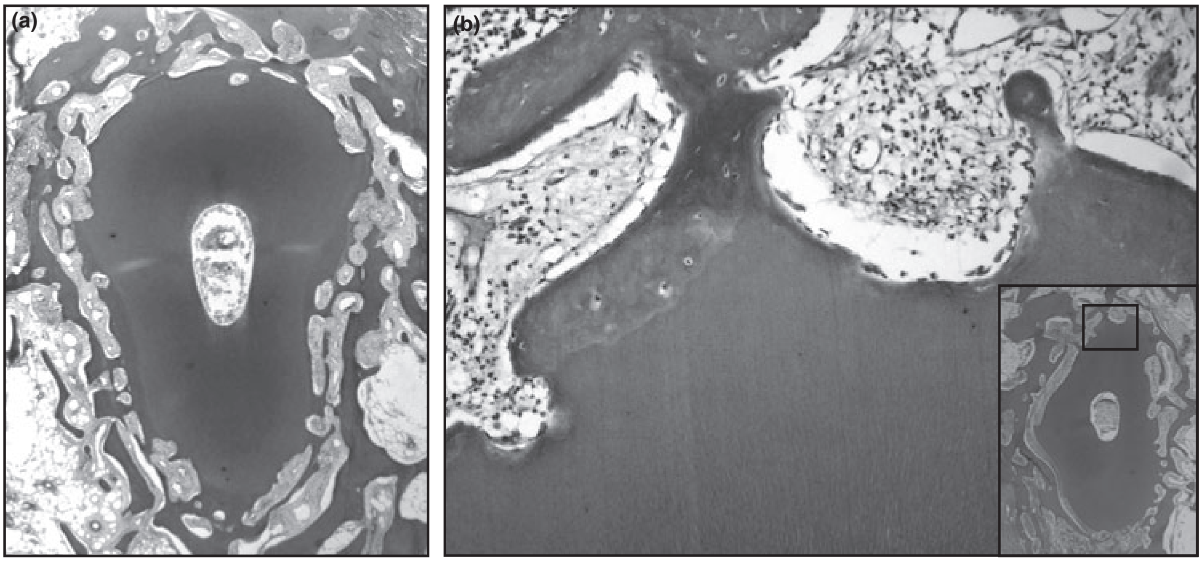

Fig. 4 (a). Histological section showing a cross section of a root treated with bisphosphonate, showing extensive replacement resorption (H&E, original magnification 20×). (b). Bony union to previously resorbed dentin, with inflammatory cells present in the adjacent periodontal ligament (H&E, original magnification 200×). Insert shows the same cross section (H&E, original magnification 20×).

bisphosphonate exerted a positive effect in reducing the inflammatory response. On the other hand, calcium hydroxide appears to exert some degree of benefit, in that inflammatory resorption and periodontal inflammation were lower in this group than in the negative control and replacement resorption and ankylosis were lower than in the bisphosphonate-treated group.

The lack of an effect of the bisphosphonate on root resorption and bone deposition could result from limited penetration through the dentinal tubules to the root surface. Despite the large excess of bisphosphonate present in the canal space, binding by chemisorption of the bisphosphonate to hydroxyapatite crystals within the tubule walls may have prevented an effective concentration of the drug at the root surface. We did not attempt to measure the rate or extent of etidronate diffusion through dentin. Regardless of the reason for lack of response, it is clear that the use of the canal space as a reservoir for bisphosphonate delivery to the root surface is not an effective approach to preventing replacement resorption.

Measures to optimize periodontal ligament cell survival through appropriate moist storage currently appear a more productive approach to the problem of replacement resorption (8–10). Improved storage media, in association with better public awareness of immediate post-trauma management, should result in better clinical outcomes than extensive management of the dehydrated avulsed tooth before replantation.

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