Clin Oral Invest (2006) 10: 77–83
DOI 10.1007/s00784-005-0032-1

ORIGINAL ARTICLE

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Tissue responses to an experimental calcium phosphate cement and mineral trioxide aggregate as materials for furcation perforation repair: a histological study in dogs

Received: 6 August 2005 / Accepted: 21 December 2005 / Published online: 1 February 2006

Abstract The aim was to evaluate histologically the inflammatory reactions and tissue responses to an experimental tricalcium phosphate cement (TCP) and mineral trioxide aggregate (MTA) when used as repair materials in furcation perforations in dogs. Perforations were performed in 24 mandibular premolars of six anaesthetised dogs and filled either with ProRoot MTA (grey) or TCP. The root canals were subsequently shaped and filled, and the access cavities were closed with a bonded composite resin. The animals were killed at 12 weeks. After radiological examination, the teeth and surrounding structures were processed for light microscopy. Concerning the grades of inflammation, MTA exhibited significantly better results than TCP (chi-square test according to Pearson). No furcation was free of inflammatory cells. Mild inflammation was observed in nine of twelve cases with MTA and only twice in those with TCP. No significant differences were revealed between MTA and TCP in terms of bone reorganization or deposition of fibrous connective tissue (Mantel-Haenszel chi-square test). The grade of radiological examination corresponded with the grade of inflammation or differed by only one grade plus or minus. Perforations located in the furcation of teeth remain an endodontic and a periodontal problem with an uncertain prognosis, in spite of the promising modern materials applied.

Keywords Biocompatibility · Calcium phosphate cement · MTA · Perforation · Tissue responses

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Introduction

In some cases, root perforations can result from resorptions and carious lesions. However, this incident usually occurs during endodontic treatment and preparations for a post [1]. The prognosis of a root perforation depends on its size and location, the length of time the defect has been open to the environment before sealing and the amount of periodontal irritation. The shorter the time lapse, the smaller the size and the more apical the perforation, the greater is the chance for successful treatment [5].

Of the two repair methods used, surgical and non-surgical, the latter has recently been favoured because – due to the access preparation – this treatment is not associated with iatrogenic bone loss [1]. Furthermore, surgical repair is not possible at all locations (e.g. lingual side of mandibular molars, trifurcations) [8].

In addition to the correct treatment regimen, the properties of the repair material are important. The ideal material should be able to seal the defect and should have excellent biocompatibility. Furthermore, induction of osteogenesis and cementogenesis, ease of handling and a low product price are advantageous [9, 16].

Since 1998, mineral trioxide aggregate (ProRoot MTA; Dentsply/DeTrey, Konstanz, Germany) has been available. This product is indicated for the reparation of various root defects, apexification and direct pulp capping. Several in vitro and in vivo experiments have shown that MTA prevents leakage, is biocompatible and promotes regeneration of the original tissues when placed in contact with dental pulp or periradicular periodontium [11, 20, 25].

Calcium phosphate cements (CPCs) are another group of materials that may be suitable for repairing root perforations. CPCs were developed as a mouldable treatment modality that chemically bonds to the host bone, restores contour and augments the biomechanical properties of the injured or reconstructed region [15, 23]. A self-setting cement, incorporating tetracalcium phosphate (TTCP) and dicalcium phosphate dihydrate (DCPD) or anhydrous (DCPA) as the major components, was first reported by Brown and Chow in 1986 [23].

In the following years, lots of further cements have been developed and studied. Common components besides TTCP, DCPD or DCPA are monocalcium phosphate monohydrate (MCPM) and anhydrous (MCPA), octacalcium phosphate (OCP), tricalcium phosphate (TCP), hydroxyapatite (HA) and fluoroapatite (FA), with different additives like carbonates, sulphates or metallic oxides. Water, calcium- or phosphate-containing solutions, organic acids or aqueous solutions of polymers are used as cement liquids. The primary role of the liquid is to provide a vehicle for the dissolution of the reactants and precipitation of the products, although it may sometimes contain a reactant for the cement setting reactions [6]. Some of the CPCs were also successfully used and tested as endodontic (sealer) and periodontal materials (bone cements) [12, 27].

With regard to furcal perforations, healing is difficult at this location and bacteria are likely to penetrate the defect via the gingival sulcus and the periodontal ligament. Therefore, this kind of perforation represents the greatest challenge for all materials used in this situation, although CPCs seem to be a promising alternative because of their properties regarding biocompatibility, sealing and handling.

Therefore, the aim of this study was to examine the inflammatory reactions and tissue responses of a recently developed CPC compared with grey MTA as materials for the repair of furcation perforations in dogs.

Materials and methods

This study involved 24 mandibular premolars in six adult (2 to 4 years old), mixed breed dogs (10 to 15 kg body weight). Animals were included only if clinical examination revealed intact dentitions and an absence of pre-existing periodontal breakdown in the furcation regions. All animal experimentations were approved and reviewed by the University of Istanbul, Turkey, and were in accordance with the ethical guidelines of the Ethics Committee of the Faculty of Dentistry. The principles of laboratory animal care (NIH publication No. 86-23, revised 1985) were followed.

Anaesthesia: A combination of xylazine (20 mg/10 kg) and ketamine (30 mg/10 kg) was used. Anaesthesia was maintained by subsequent injections of ketamine and was controlled by a veterinarian.

Perforation creation: Mandibular P2 and P3 in each of the two quadrants were used in this study. After rubber dam application and disinfection of the crown (chlorhexidine digluconate), access to the pulp chambers was gained with a sterile water-cooled carbide bur. After a pulpotomy, pulp tissue was extirpated with Hedström files. The root canals were irrigated with sodium hypochlorite (1%) and chlorhexidine digluconate (0.2%) and dried with sterile paper points. Then a sterile round bur (ISO size 012) was used to perforate the pulp chamber floor in the furcation until haemorrhage was noted (perforation diameter was equivalent to round bur).

Perforation repair: To repair the perforations, two different cements were used. Each P2 on the left and each P3 on the right mandibular side was filled with grey ProRoot MTA, while the perforations of the left third and right second premolars were sealed with an experimental CPC (Augmentech AT, Wetzlar, Germany). The powder consisted of TCP, magnesium phosphate, magnesium hydrogen phosphate and strontium carbonate. The liquid was a watery solution of diammonium hydrogen phosphate. Both cements (MTA and TCP) were prepared according to the manufacturers' instructions, placed into the perforation defects and compacted with a plugger.

Subsequently, the root canals were shaped with reamers and Hedström files (apical master file ISO size 35, electrometrically controlled with Root ZX; J. Morita Europe GmbH, Dietzenbach, Germany), dried with sterile paper points and filled with the experimental TCP. For bacteria-tight sealing of the access cavities, the chemically cured composite resin Clearfil Core New Bond (Kuraray, Osaka, Japan) was used after conditioning of and bonding to enamel and dentine.

Postoperative period: The dogs were kept inside the clinics of the Faculty of Veterinary Medicine, University of Istanbul, under continuous monitoring of weight and food intake. After 12 weeks, the animals were sacrificed by an overdose of sodium pentobarbital. The lower jaws were ex-articulated, prepared free from soft tissues and fixed in buffered formalin (10%).

Radiological examination: The mandibles were cut in the median sagittal plane. X-ray examinations were made of the treated premolars. The radiological evaluation was performed by an experienced dentist unaware of the different experimental groups. The objective was to determine whether a radiolucency of the furcal region bordering the repaired perforations could be detected. The scoring criteria were as follows:

Grade 1
No indication of bone loss
Grade 2
Minor bony defect (furcal radiolucency in vertical dimension between roots <0.5 mm)
Grade 3
Medium bony defect (0.5 to <1 mm)
Grade 4
Major bony defect (≥1 mm)

Histological preparation and examination: For the preparation of histological sections, the cutting–grinding technique was used [7]. The premolars with surrounding periodontium were sectioned with a diamond band saw into blocks (about 20×13×4 mm). The blocks were dehydrated with ethanol (from 70 to 100%), infiltrated with methyl methacrylate (Merck KG, Darmstadt, Germany) and stuck to a holding fixture parallel to the favoured section plane. Serial sections showing each tooth in a mesiodistal direction (stuck to slides) were made with an internal edge radial saw. All sections were polished to a thickness of 20 μm.

After staining in haematoxylin and eosin, that section of each tooth representing the largest contact zone between the repair material and the periodontium was identified and used for histological examination by light microscopy. Histological evaluation was performed by a pathologist unaware of the experimental groups. The following parameters were examined:

(a) amount of inflammatory cells,
(b) deposition of connective tissue and
(c) bone reorganization.

Grading the parameter "amount of inflammatory cells" was performed according to Ørstavik and Mjör [19]:

Grade 1
No cells detectable
Grade 2
Mild (few scattered inflammatory cells)
Grade 3
Moderate (focal accumulation of inflammatory cells)
Grade 4
Severe (dense infiltration of inflammatory cells)

The composition of the inflammatory cells (lymphocytes, plasmacytes, granulocytes and macrophages) allowed for classification of the inflammation type.

The parameters "deposition of connective tissue" and "bone reorganization" were classified as follows:

Grade 1
None
Grade 2
Mild
Grade 3
Moderate
Grade 4
Severe

For statistical analysis, the results of "amount of inflammatory cells" were evaluated using the chi-square test according to Pearson ($p \leq 0.05$), whereas "deposition of connective tissue" and "bone reorganization" were evaluated using the Mantel-Haenszel chi-square test (test for linear by linear association; $p \leq 0.05$).

Results

All 24 treated teeth were included for radiological and histological examinations.

Radiological examination: In six cases of MTA and three of TCP, no bone loss was found in the furcation. Minor bony defects were observed three times in contact with MTA fillings and twice in contact with TCP fillings (Fig. 1). A medium bony defect relating to MTA was evaluated once only, compared to two cases relating to TCP. Major bony defects were found at two MTA-treated and five TCP-treated teeth.

Histological examination: Concerning the grade of inflammation, MTA exhibited significantly better results than TCP ($p=0.004$; chi-square test according to Pearson), but no furcation was free of inflammatory reactions. Mild inflammation was observed in nine of twelve cases with MTA and only twice in those with TCP; the cell composition provided the basis for the classification of the inflammation type (Table 1). No significant differences were revealed between MTA and TCP in terms of bone reorganization ($p=0.304$) or deposition of fibrous connective tissue ($p=0.744$; Mantel-Haenszel chi-square test; Tables 2 and 3). A few specimens had to be classified between the grades 1, 2, and 3 (as 1.5 or 2.5).

Representative examples depicting inflammatory reactions and tissue responses (formation of connective fibrous tissue, osteogenesis and bone resorption) after application

Fig. 1 Representative examples of minor bony defects (left tooth MTA, right tooth TCP, not radio-opaque) in the furcation (dog 6, right P2 and P3)

Table 1 Number of perforations treated with mineral trioxide aggregate and calcium phosphate cement with respect to grades and types of inflammation

Grade	Inflammation (number)									
	Mineral trioxide aggregate					Calcium phosphate cement				
	Acute	Chronic	Recidiv	N. class	Total	Acute	Chronic	Recidiv	N. class	Total
2	0	3	0	6	9	0	1	0	1	2
3	0	1	2	0	3	0	1	9	0	10

Recidiv Recidivating, *N. class* not classifiable

Table 2 Deposition of connective tissue with respect to intensity (grade)

Grade	Deposition of connective tissue (number)	
	MTA	CPC
2.0	9	10
2.5	3	0
3.0	0	2

Table 3 Bone reorganization with respect to intensity (grade)

Grade	Bone reorganization (number)	
	MTA	CPC
1.0	3	0
1.5	0	2
2.0	8	9
2.5	1	1

of MTA and TCP, respectively, are demonstrated in Figs. 2, 3, 4, 5, 6, 7 and 8.

All specimens exhibited slight overfilling. No direct contact to the underlying bone and therefore no ankylosis was observed in any of the specimens. Even in cases with mild inflammation, there was a thin layer of connective tissue between repair material and bone (Figs. 2, 3 and 4). No eosinophile granulocytes were found.

Discussion

Dental literature provides lots of study designs for the evaluation of the biocompatibility or efficacy of materials for root repair. Examinations range from in vitro tests to clinical case reports. Only one clinical study in which teeth with surrounding periodontium were removed for histological examination can be found in the literature [14]. However, that study is no longer relevant because the materials (ivory and jodoform) are no longer used nowadays.

The dog is a demanding experimental model, having two rooted lower premolars that often furcate as close as 1 to 2 mm from the cementoenamel junction. As a result, epithelialization and the formation of connective tissue at a furcation perforation should be more likely than in humans, where the furcation lies deeper within the alveolus. Thus, any technique shown to produce favourable results in dogs may have a more favourable response in humans, where the distance from the cementoenamel junction to the furcation is greater [21]. Thus, it was not surprising to see epithelial proliferation and connective tissue in cases of inflamed furcations.

Contrary results in the literature can be found for perforation repair with traditional materials. Unsatisfactory biocompatibility was recorded in various studies with amalgam, Cavit, calcium hydroxide, indium foil, TCP ceramic, hydroxy apatite or gutta-percha [3, 4, 8], while Himel et al. [10] as well as Sinai et al. [24] noted mild inflammatory reactions in cases with TCP ceramic treated perforations.

In the present study, MTA was used as a comparison material because of its favourable sealing abilities and high biocompatibility [11, 20, 21, 25]. Due to ethical considerations to use and kill dogs as little as possible, a negative control group was renounced. Various published studies show that untreated root defects and perforations that are allowed to remain open to saliva have an extreme poor

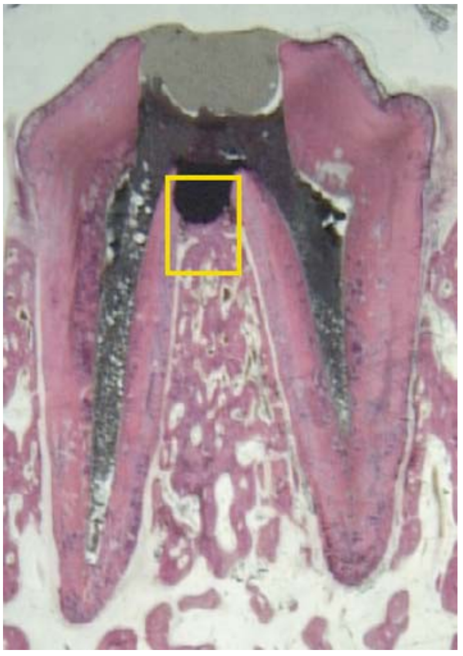

Fig. 2 Overview micrograph as a representative example of a mild inflammatory reaction. The bone in the furcation seems to have direct contact with the filling material in this magnification (haematoxylin–eosin, dog 5, right P3, MTA)

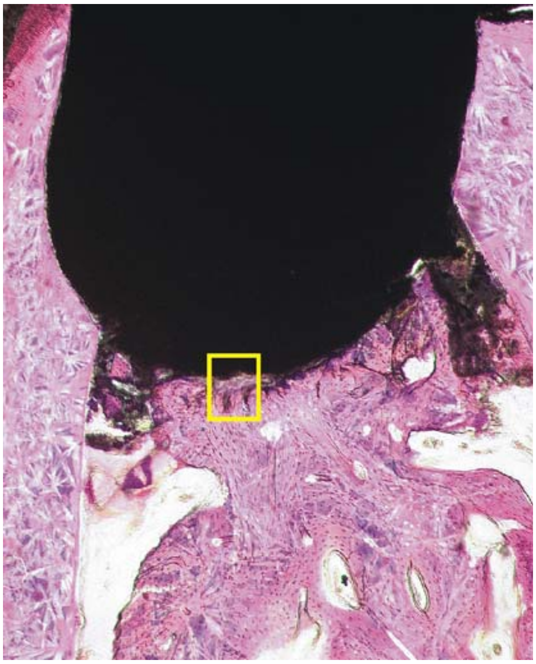

Fig. 3 No inflammatory infiltration is detectable (objective magnification ×2, dog 5, right P3, MTA)

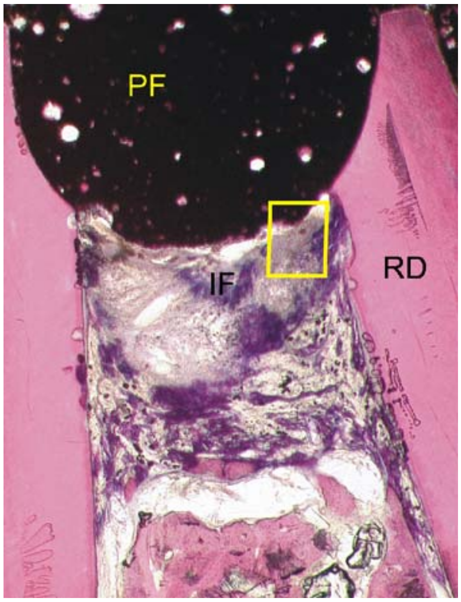

Fig. 5 Overview micrograph of a furcal region with a focal accumulation of inflammatory cells (haematoxylin–eosin, objective magnification ×2, dog 1, right P2, TCP). *IF* Inflammatory infiltration, *PF* perforation filling material, *RD* root dentine

prognosis and are associated with severe inflammatory reactions [8, 21].

Randomization regarding the materials for perforation repair appeared to be inessential. Several studies have shown that there is no particular relationship between tooth type or width and success rate of perforation repair [22, 26]. Thus, sealing of equal numbers of perforations of second and third mandibular premolars with TCP and MTA, respectively, was performed.

Costs and ethical considerations are limitation factors of studies using animals. Notwithstanding, it is clear that the more samples per group are used, the greater is the power of the statistical analyses. However, the sample size of the present study (n=12) corresponded to Yildirim et al. [26],

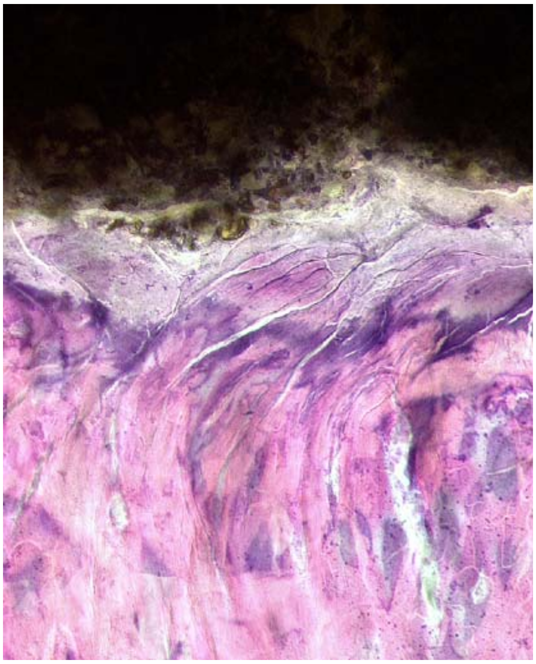

Fig. 4 In this magnification, a very thin layer of connective tissue between bone and filling material can be found with only a few inflammatory cells (objective magnification ×40, dog 5, right P3, MTA)

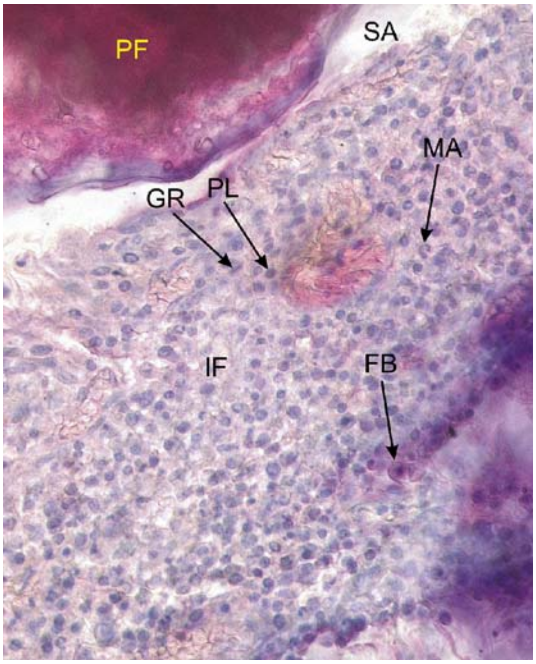

Fig. 6 Various inflammatory cells are visible (objective magnification ×40, dog 1, right P2, TCP). *FB* Fibroblast *GR* granulocyte *IF* inflammatory infiltration *MA* macrophage *PF* perforation filling material *PL* plasma cell *SA* shrinkage artefact

Fig. 7 Overview micrograph of a furcal region as a representative example of bone reorganisation (haematoxylin–eosin, objective magnification ×2, dog 1, right P2, TCP)

while Pitt Ford et al. [21] worked with only six to eight samples per group and evaluation time.

Furcal perforation was chosen, on the one hand, because of its critical prognosis ("worst case") [1, 5]. On the other hand, the frequency of this kind of perforation is high (while searching for root canals on the pulp chamber floor, or while shaping the root canals as in so-called stripping perforations) compared to other locations, and the application of the repair material can be well controlled by the dentist. However, extrusion of the material into the periodontium usually cannot be avoided. The matrix concept should prevent this by using bioinert matrices under sealing materials, but this procedure is complex and does not guarantee success. Moreover, some tested matrices have decreased the sealing ability of the material, while others have not satisfied the criteria of biocompatibility [2, 16].

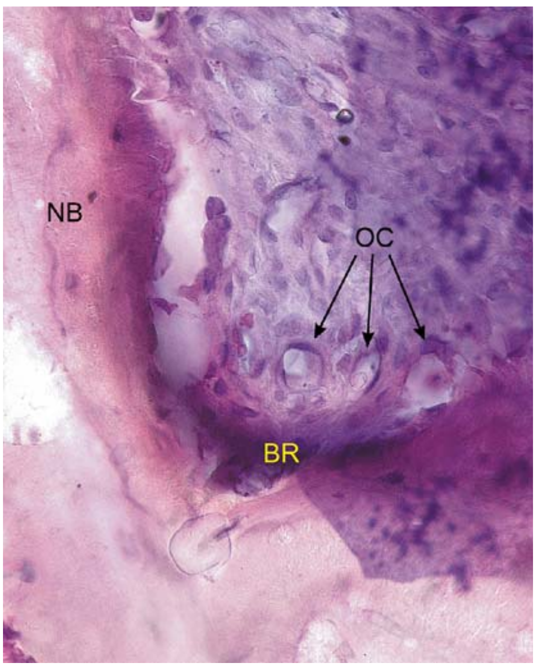

Fig. 8 Zones of newly developed bone and bone resorption (with osteoclasts) can be observed (haematoxylin–eosin, objective magnification ×40, dog 1, right P2, TCP). *BR* Bone resorption *NB* new bone *OC* osteoclast

In the present study, radiological examination was only performed to provide an additional source of information relating to biocompatibility (without statistical analysis) for the following comparison with histological results. With the exception of one case (dog 6, left P3), the grade of radiological examination (Fig. 1) corresponded with the grade of inflammation of the same tooth, or differed by only one grade plus or minus. Therefore, radiographs can be recommended for the assessment of inflammation levels in a furcation, in particular at mandibular molars.

For histological evaluation, basically two different procedures are possible. On the one hand, teeth can be demineralised and processed by standard paraffin embedding procedures for examination by microscopy and immunohistochemistry. However, artefacts at the border zone between hard and soft tissues are not always avoidable. On the other hand, the cutting–grinding technique after methyl methacrylate embedding can be used, as in the present study, which affords an excellent examination of hard tissues without demineralisation (Figs. 7 and 8) [7]. It should be emphasised that each histological result represents the situation at the time of euthanasia, making high precision in the immunohistochemistry inessential.

The histological evaluation showed that no furcation in either group was free of inflammatory cells. Thus, the present study could not confirm (Figs. 2, 3, and 4) the very high biocompatibility of MTA observed in other examinations [17, 25]. The grades of inflammation in cases sealed with TCP were marginally but significantly higher (Figs. 5 and 6), whereas concerning tissue reactions, the experimental CPC showed a very similar outcome. The lowest grade (1) means that no deposition of connective tissue and no bone reorganization could be detected by microscopy, whereas grade 4 reflects high densities of the mentioned parameters; such cases were preceded by intensive inflammatory reactions and/or traumatic incidents.

Holland et al. [11] found, in a study with dogs, varying tissue reactions in contact with MTA after 30 days, while after 180 days, the periodontium was almost free of inflammation. However, lateral perforations (representing a better prognosis) were sealed in that study. The above-mentioned study allows the speculation that better results might be observed after a longer postoperative period. It is known that calcium phosphate-containing materials like CPCs or MTA initially induce inflammatory reactions (necrosis) in different tissues, but the period of time this situation persists for and the time of the beginning of the healing phase have not been finally evaluated.

The experimental calcium phosphate cement used in the present study is still in the developmental stage. Thus, qualitative and quantitative modifications could enable an even higher biocompatibility (particle size of the cement powder, concentration of the cement liquid, pH value, etc.) [13, 18]. Repair reactions with newly formed bone could be observed in some cases (Figs. 7 and 8) but were not consistent for all teeth. Therefore, further investigations are clearly warranted.

Conclusion

Perforations located in the furcation of teeth remain both an endodontic and a periodontal problem with an uncertain prognosis in spite of the promising modern materials used, as loss of bone and the formation of connective tissue, although to varying extents, could be detected in most of the specimens.

Acknowledgements The authors thank Dr. Harald Ebhardt, Institute for Pathology, Charité - Universitätsmedizin Berlin, Germany, for photographing of the histological sections.

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