

Human pulps capped with PDGF: A pilot study

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Abstract

Objective

Growth factors have shown the potential to promote odontoblast-like cell differentiation and induce the formation of reparative dentin. The aims of this pilot study were to develop a regenerative approach to pulp capping using platelet-derived growth factor (PDGF) BB and to describe histologically the pulp tissue response.

Materials and methods

Two third molars (Site A and Site B) were treated. Class I cavities were prepared and the exposed pulps were capped with cotton pellets embedded in a PDGF solution. Teeth were extracted after 40 days and processed for routine histological examination. The hard bridge formation and the pulp reaction were evaluated.

Results

In Site A, incomplete and thick dentin bridge formation was observed. The pulp tissue close to the remaining exposed pulp was moderately disorganized, with many fibroblasts and few inflammatory cells. In Site B, an incomplete dentin bridge covered part of the defect. The pulp was overall normal, but a limited area showing a clot-like tissue with many fibroblasts and few inflammatory cells close to the dentin bridge interruption was observed.

Conclusion

PDGF-BB did not elicit an inflammatory response and did not induce extensive dentin matrix deposition. It thus appears to be a safe pulp capping agent.

Keywords

Histology, human platelet-derived growth factor, pulp capping, wound healing.

Introduction

The dental pulp provides nutrition and sensory properties to dentin and has reparative capacity to react to injury. When the injury results in odontoblast death, a new generation of odontoblast-like cells may differentiate from progenitor cells within the pulp and secrete a reparative dentin matrix.¹ Pulp capping is a common procedure that induces reparative dentin formation after pulp exposure due to cavity preparation, caries removal or trauma. Calcium hydroxide, zinc oxide eugenol cements, composite resins, mineral trioxide aggregate (MTA) and glass ionomer cements are used in clinical daily practice.^{2, 3} However, several concerns have been listed regarding the use of these materials for pulp capping, including cytotoxic effects,⁴ the lack of adequate bleeding control after acid etching⁵ and the new hard-tissue formation at the expense of pulp chamber width, causing narrowing of root canals.⁶ Although calcium hydroxide is the most widely used pulp capping agent to encourage hard-tissue bridging, the material is not able to effectively induce new tissue formation.⁷ Bridge formation remains unpredictable, with varying thickness and numerous tunnel defects,⁸ suggesting that it may be of insufficient quality to protect the pulp against bacterial microleakage along the restoration margins. Several articles have addressed the use of MTA for pulp capping and demonstrated a hard-tissue barrier beneath the MTA; however, pulpal soft tissue enclosed within the hard-tissue barrier and unpredictable dentin bridge formation were observed.^{9, 10}

Recently, a growth factor delivery approach has been introduced to induce reparative dentin formation in noninflamed mechanically exposed pulps.^{11, 12} Rutherford et al. examined histologically the reparative dentin formation of pulp treated with osteogenic protein-1 (bone morphogenetic protein [BMP] 7) in monkeys.¹³ They reported that BMP-7 has the potential to induce the formation of reparative dentin and related the amount of newly formed dentin to the amount of implanted protein. Nakashima observed histologically the induction of tubular dentin formation in teeth capped with BMP-2 and -4 in monkeys.¹¹ An *in vivo* study has demonstrated with histomorphometric analysis the role of transforming growth factor- β in promoting odontoblast-like cell differentiation and the secretion of extracellular matrix.¹⁴ The effects of enamel matrix protein on pulp capping have been evaluated histologically and immunohistochemically in

animal¹³ and human studies.^{15, 16} After application of enamel matrix protein, the damaged pulp showed at first a reparative process with formation of a scar and moderate inflammatory infiltrate. Subsequently, neogenesis of normal dental pulp occurred and odontoblast-like cells produced reparative dentin.¹⁷ In the literature, there is converging evidence that reparative processes recapitulate early developmental events that lead to dental tissue formation.¹⁸ However, the effects of platelet-derived growth factor (PDGF) on reparative processes after pulp capping have not been defined. PDGF is a potent mitogenic, chemotactic agent. It stimulates cells of mesenchymal origin to produce protein¹⁹ and promotes angiogenesis and the regeneration process of several tissues, such as bone, cementum and periodontal ligament.²⁰ PDGF also regulates cell proliferation and dentin matrix protein production in dental pulp culture.^{21, 22} In their histochemical and immunohistochemical study, Yokose et al. evaluated the effects of three PDGF dimers (PDGF-AA, -BB and -AB) on odontoblast differentiation of dental pulp cells.²³ The authors reported the different effects of the PDGF dimers on dentin formation during the repair process in damaged dental pulp. They observed that PDGF-AB and -BB stimulated the differentiation of odontoblastic cells, increasing the number of mature odontoblastic cells. In contrast, PDGF-AA exerted inhibitory effects on odontoblast differentiation.²³ These findings suggest a role of PDGF-BB in dentinogenesis in the dental pulp and in differentiation of odontoblasts during repair processes after injury to the mature pulp. The aims of this preliminary human study were to develop a regenerative approach to pulp capping using PDGF-BB and to describe histologically the pulp tissue response.

Materials and methods

After a thorough explanation of the experimental rationale, clinical procedure and possible risks, written informed consent was obtained from both subjects to be entered in the study. The study conformed to the principles outlined in the Declaration of Helsinki of 1975, as revised in 2013, on experimentation involving human subjects and was approved by the Ethics Committee of the Department of Human Morphology and Biomedical Sciences "Città Studi", Milan, Italy. Before treatment, all patients gave written informed consent. Two completely erupted third molars that needed to be extracted for orthodontic treat-

ment were selected from two patients (one tooth from each patient) with the following inclusion criteria: (a) no systemic diseases or metabolic bone disorders; (b) not pregnant; and (c) no history of malignancy, radiotherapy or chemotherapy for a malignancy in the past five years. Furthermore, in order to standardize the age-related prognostic factor, subjects aged between 18 and 39 were enrolled.²⁴ The experimental teeth were clinically and radiographically examined and presented superficial enamel decay; however, the teeth were asymptomatic, without periapical lesions and responded positively to the cold stimulus test performed by applying HYGENIC ENDO-ICE F frozen gas (Coltène/Whaledent, Mahwah, N.J., U.S.) for 5 s to the buccal surfaces.

Procedures employed

Forty days before the extraction, after local and intraligament anesthesia with lidocaine containing 1:80,000 epinephrine to control pain and bleeding from the exposed pulp, the selected molars were isolated with a rubber dam and disinfected with topical antiseptic. Class I cavities on the occlusal surfaces of the experimental teeth were prepared by means of diamond burs (1 mm in diameter) and the pulps were exposed. On one tooth (Site A), a perforation of 1 mm × 1 mm (evaluated at the level of the pulp chamber) was performed; and on the other tooth (Site B), the perforation was 3 mm × 3 mm.

After rising with sterile water to remove the debris, establishing hemostasis with a sterile cotton pellet soaked in saline solution and drying with a sterile cotton pellet, the pulp was capped with sterile cotton embedded in a PDGF-BB solution and covered with zinc oxide cement (CAVIT, 3M ESPE, Seefeld, Germany). During the days after capping, the patients completed a questionnaire on pain occurrence. After 40 days, the experimental teeth were tested for pulp vitality by applying HYGENIC ENDO-ICE F and were carefully extracted without root separation or crown fracture.

Histological analysis

Immediately after extraction, the teeth were immersion fixed in a 10% formalin/0.1 M phosphate-buffered saline (pH 7.4) for 24 h at room temperature. The dental crown was separated from the roots using a round bur in a low-speed

handpiece and then decalcified for 30 days in a solution containing formic acid (625 cm³ in 625 cm³ of distilled/purified water) and sodium citrate (250 g in 125 cm³ of distilled/purified water). Decalcification of dental tissue was verified by radiograph. After rinsing under running water for 48 h, the sample was routinely dehydrated in increasing concentrations of ethanol (from 50 to 100%), immersed in xylol for 12 h and then embedded in paraffin. Serial buccolingual sections were obtained from 4 to 5 mm and then hydrated in xylol and decreasing concentrations of ethanol (from 100 to 70%) and finally immersed in distilled water. Sections were stained with hematoxylin and eosin (H&E) to evaluate the tissue morphology and with Masson's trichrome stain to distinguish the connective matrix from cells. The sections were viewed and photographed under a light microscope (Eclipse E600, Nikon, Tokyo, Japan) equipped with a calibrated digital camera (DXM 1200, Nikon). Multiple central sections were used to perform an overall assessment for each tooth. The hard-tissue bridge formation (continuity, morphology, localization and thickness) and the dental pulp reaction (inflammatory cell response and tissue disorganization) were described.

Results

Both patients (A and B) who completed the study were female, nonsmokers, and 23 and 26 years old, respectively. A total of two teeth were analyzed. After the experimental pulp capping, the patients did not report any symptoms or analgesic intake. At the extraction appointment, both teeth were vital and both cavities still closed with CAVIT. At the histological evaluation, the thickness (mm) of the newly formed hard tissue was measured at three different points of the bridge: alongside the dentinal wall (on the mesial side and distal side) and in the center. **Table 1** shows the mean thickness of the newly formed bridge.

Site A

In all of the sections, the drill-created cavity contained debris and bacteria along all of the cavity walls (**Fig. 1**). An incomplete dentin bridge lined the pulp exposure site and was formed by well-organized tubular reparative dentin, with a clear predentin layer and odontoblastic-like cells (**Fig. 2**). No extensive dentin matrix deposition

Table 1

	M [†]	Center	D [‡]
Site A	209	190	–
Site B	–	338	92

[†] M = mesial side.
[‡] D = distal side.

Table 1
 Thickness (mm) of the newly formed bridge measured at three different points. The thickness was not evaluated in sites where the bridge was absent.

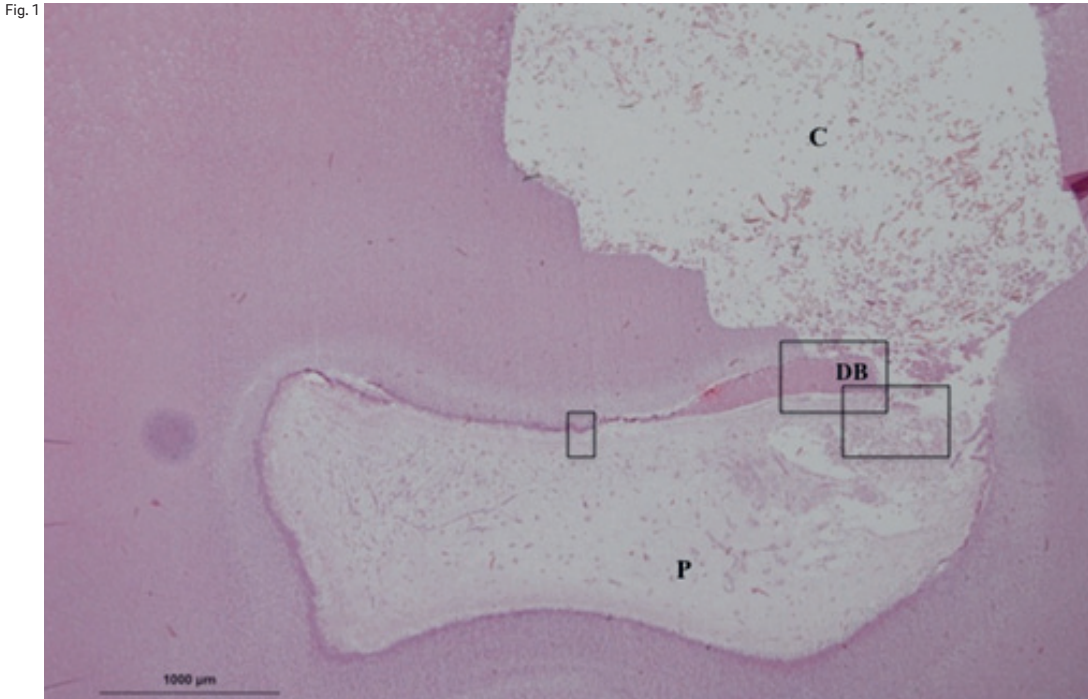


Fig. 1
 Photomicrograph of Site A. Buccolingual section. The drill-created cavity (C) containing much debris is separated from the pulp (P) by a thick and incomplete dentin bridge (DB). The newly formed hard tissue starting from the original dentin tissue covers only half of the exposed pulp. H&E staining (at original 20x magnification).

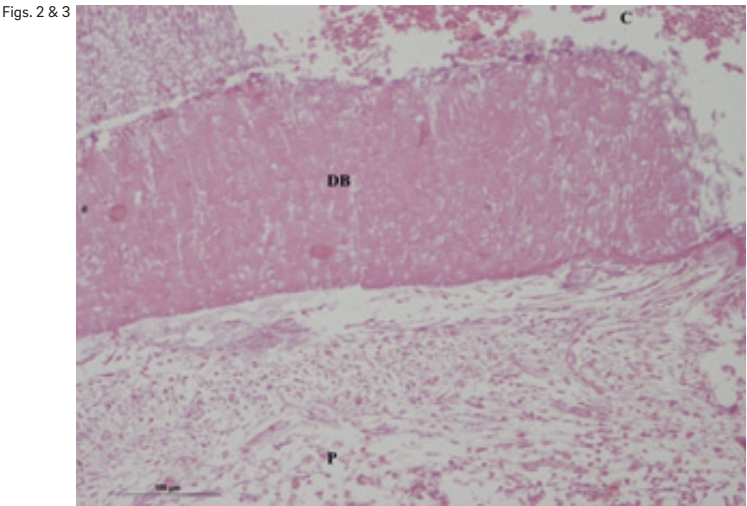


Fig. 2
 Detail of **Figure 1**. The dentin bridge (DB) is formed by tubular and well-oriented reparative dentin. The pulp (P) appears slightly disorganized with few scattered inflammatory cells. C = cavity. H&E staining (at original 100x magnification).

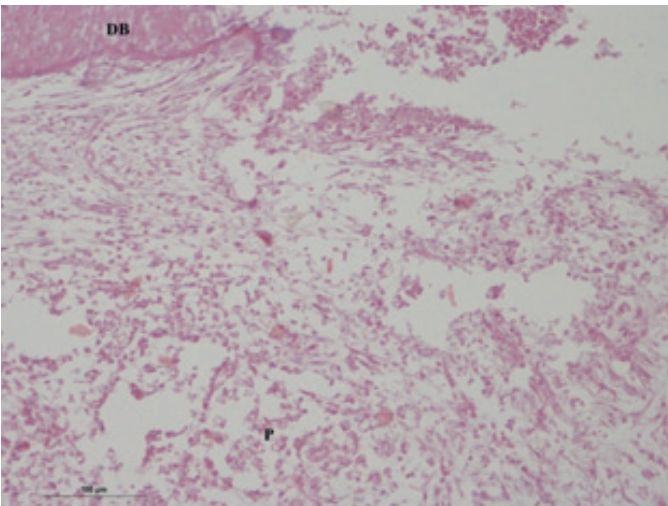
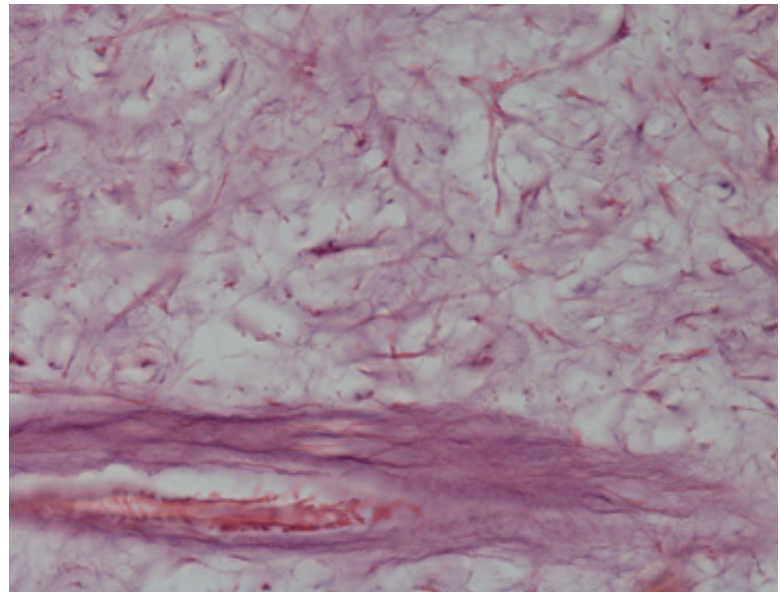
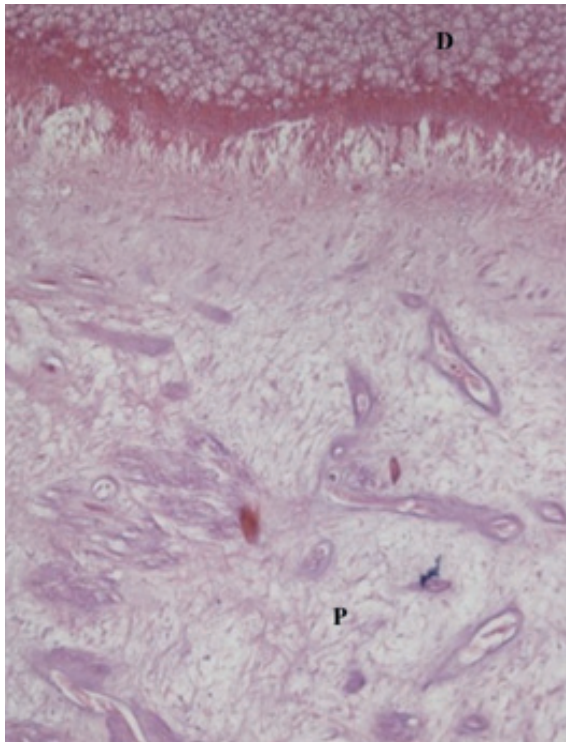


Fig. 3
 Detail of **Figure 1**. The pulp tissue (P) close to the newly formed dentin (DB) and surrounding the remaining defect appears disorganized, with many fibroblasts and few scattered inflammatory cells. H&E staining (at original 200x magnification).



Figs. 4 & 5

Fig. 4

Detail of **Figure 1**. The pulp tissue (P) adjacent to the reactive area and under the original dentin (D) appears healthy and well organized, with no signs of necrosis or abscess. H&E staining (at original 100× magnification).

Fig. 5

Detail of **Figure 1**. Photomicrograph of the pulp in the area adjacent to the reactive tissue. No extravasated red blood cells, suffering pulp or inflammatory cells are detectable. H&E staining (at original 400× magnification).

obliterating the pulp chamber was observed. The general state of the pulp close to the remaining defect was moderately disorganized. This area contained many fibroblasts, some extravasated red blood cells and few inflammatory cells (**Fig. 3**). No signs of abscess were observed. The pulp tissue adjacent to the reactive area appeared normal, with no signs of inflammation or necrosis (**Figs. 4 & 5**).

Site B

Debris occurred along and over the cavity walls, but without touching the pulp tissue (**Fig. 6**). The hard bridge formation was moderate and incomplete, leaving a small area of communication between the capping material and the dental pulp. The reparative dentin was tubular and well oriented (**Fig. 7**), without invading the pulp space. The general state of the pulp was normally organized without inflammatory cells beneath the dentin bridge formation. Only a limited area of tissue disorganization and pulp reaction similar to that observed in Site A was adjacent to the hard-barrier interruption and separated the normal pulp tissue from the contaminated drill-created cavity (**Fig. 8**). No tunnel-like defect appeared in any section. The hard-tissue thickness was greater in the central portion, and the thickness at the distal side was not calculated because of the interruptions (**Table 1**).

Discussion

The present pilot study was designed to evaluate the response of noninflamed mechanically exposed human pulps after capping performed using PDGF-BB. In Site A, an area of moderate disorganization was evident below the remaining pulp exposure site. In Site B, only a limited area of slight reaction was observed at the lateral side of the defect, close to the dentin bridge interruption. No signs of abscess or inflammatory infiltrate in the connective tissue were detected in either sample. The pulp was overall normal and asymptomatic, despite the use of nonsealing cement. Tubular reparative dentin and an adjacent well-organized odontoblast-like cell layer were detected in both samples. No extensive dentin matrix deposition obliterating the pulp chamber was found. In the literature, tunnel defects are often described throughout the newly formed dentin bridges of teeth capped with calcium hydroxide.⁸ In the present study, in both samples, the reparative dentin was compact and without defects. Since the aim of the present study was to assess the response of noninflamed pulp tissue after PDGF-BB treatment, no control samples were evaluated to compare the amount of newly formed dentin matrix. Also, the experiment was conducted on a limited number of cases and thus did not allow for statistical analysis. In the treated teeth, access to the pulp chamber was of two different sizes to assess the response of capped pulp tissue to varying extents of such a traumatic event.

Fig. 6

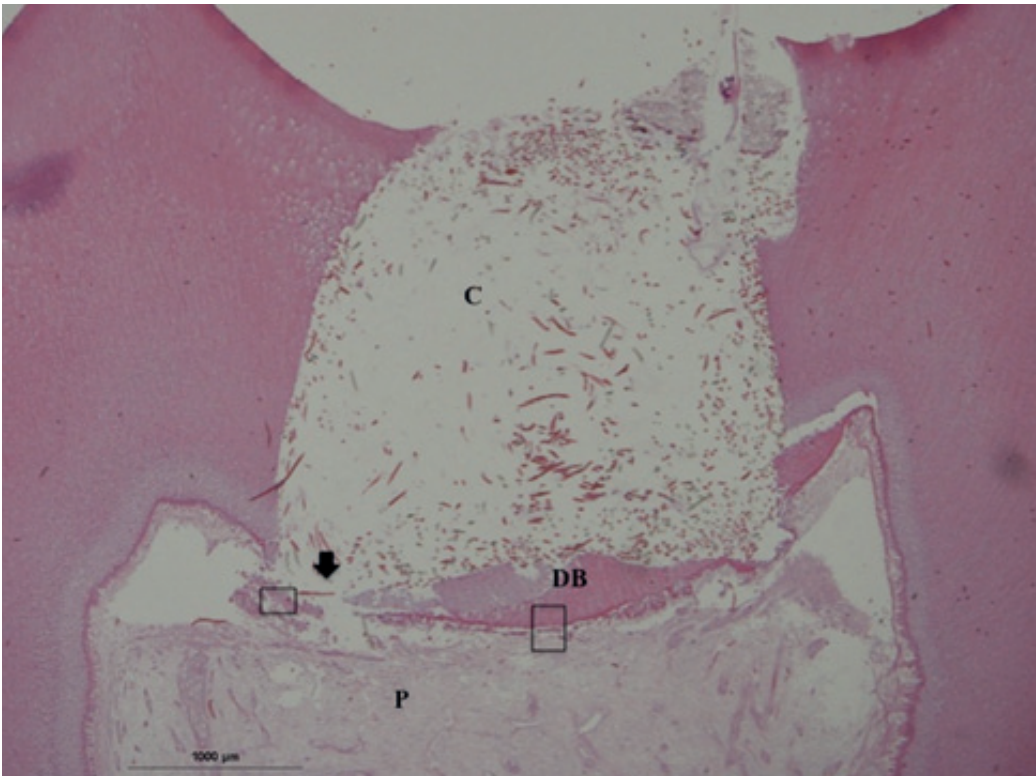


Fig. 6

Photomicrograph of Site B. Buccolingual section. Within the cavity (C), debris is visible. Between the cavity and the pulp (P), the dentin bridge (DB) runs horizontally from the cut surfaces, covering most of the exposed dental pulp. This hard tissue is very thin on the right side close to the original dentin tissue, is the thickest in the central area of the defect and is incomplete on the left side (black arrow). The dental pulp presents no inflammatory response and has an organized structure, but for the area close to the dentin bridge interruption, where a disorganized and fibrous clot-like tissue is observed. H&E staining (at original 20× magnification).

Fig. 7

Detail of Figure 6. The reparative dentin (DB) is tubular and well organized. Odontoblast-like cells (O) are between the dental pulp (P) and the predentin (PD) tissue. The pulp is well organized and without inflammatory cells. H&E staining (at original 400× magnification).

Figs. 7 & 8

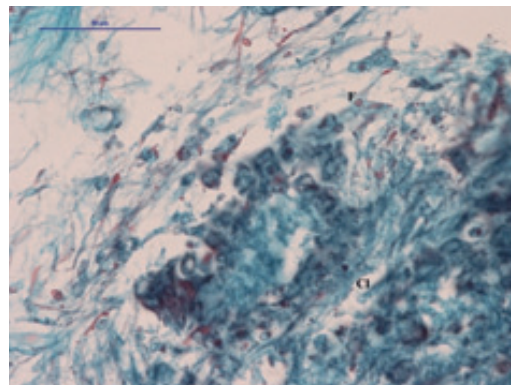
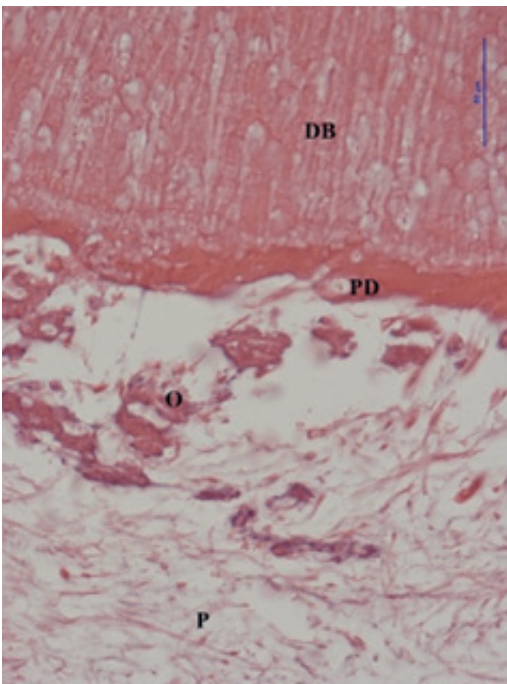


Fig. 8

Detail of Figure 6. In correspondence with the dentin bridge interruption, the pulp is not in direct contact with the cavity. A disorganized clot-like tissue (Cl) with many fibroblasts (F) and few inflammatory cells is apparent between the cavity and the pulp in close contact with bacteria and debris. Masson's trichrome staining (original 600× magnification).

These preliminary findings indicate that PDGF-BB does not elicit pulpal inflammatory response, nor induce extensive dentin matrix deposition, suggesting that this growth factor could be safely applied in human pulp capping. According to previous human models that proved the efficacy of growth factors in noninflamed exposed pulp,¹⁵ this study was performed on healthy and freshly exposed pulps. However, Rutherford and Gu demonstrated the failure of a treatment strategy utilizing BMP-7 proteins for management of inflamed pulpal wounds.²⁵ Despite this, it may be supposed that the therapeutic activity of PDGF-BB is mainly due to the promotion of tissue regeneration than to the resolution of the inflammatory process. Further studies should thus investigate the efficacy of PDGF in promoting newly formed dentin bridges in inflamed pulps and compare this treatment with a biological agent to the gold standard pulp capping agent (MTA).⁹ The role and mechanism of action of PDGF in healing of damaged dental pulp and dentin bridge formation are not completely understood. PDGF plays a role in cell chemotaxis, proliferation and differentiation at each stage of wound healing.^{19,20} In periodontics, clinical studies have been conducted since PDGF demonstrated an important role in regeneration of cementum, periodontal ligament and alveolar bone.²⁶ In a clinical trial, Nevins et al. evaluated the healing and regeneration of infrabony periodontal defects treated with highly purified recombinant human PDGF-BB and a β -tricalcium phosphate scaffold and demonstrated the efficacy of PDGF-BB in accelerating and improving periodontal soft-tissue healing and bone regeneration.²⁷ In addition, clinical trials have suggested the promotion of bone turnover during the repair process of tooth-supporting osseous defects.²⁸

A histochemical and immunohistochemical study has evaluated the effects of three PDGF dimers (PDGF-AA, -BB and -AB) on odontoblast differentiation of dental pulp cells.²³ The authors observed dentin formation during the repair process in damaged dental pulp. They also observed that PDGF-AB and -BB stimulated the differentiation of odontoblast cells, increasing the number of mature odontoblast cells. In contrast, PDGF-AA exerted inhibitory effects on odontoblast differentiation.²³ These findings suggest a role of PDGF-BB in dentinogenesis in the dental pulp and in differentiation of odontoblasts during repair processes after injury to the mature pulp. The importance of PDGF in the

dental pulp regenerative process is due to the role that this growth factor plays during embryonic development. PDGFs and platelet-derived growth factor receptors (PDGFRs) play a role in gastrulation,²⁹ development of the cranial and cardiac neural crests,³⁰ and formation of the palate.³¹ Studies have shown that PDGF- α and PDGFR- α are expressed in developing mouse molars, regulate epithelial–mesenchymal interaction during mammalian tooth morphogenesis, and have a critical function in differentiation of dental pulp cells and in the development of dental cusps.^{31,32}

Conclusion

Within its limitations, this study suggests that PDGF-BB appears to be a safe pulp capping agent. PDGF-BB may stimulate dentinogenesis, promoting differentiation of odontoblasts after dental pulp injury. It appears that differentiated odontoblasts produce tubular and compact reparative dentin, without tunnel defects, and do not obliterate the pulp chamber.

Competing interests

The authors declare that they have no competing interests.

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