Bioceramic Materials for Vital Pulp Therapy

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1 Introduction

Recent research advances demonstrating that the dentin–pulp complex is capable of repairing itself and regenerating mineralized tissue offer hope of new endodontic treatment modalities that can protect the vital pulp, induce reactionary dentinogenesis, and stimulate revascularization [1]. The dental–pulp is a complex and highly specialized connective tissue that is enclosed in a mineralized shell and that has a limited blood supply. These are only a few of the many obstacles faced by clinicians and researchers seeking to devise new therapeutic strategies for pulp regeneration.

The primary aim of pulp capping is to protect the underlying tissue from any external stress, especially bacteria. The quality of the filling and its seal are, therefore, of the utmost importance. For many years, this seal was thought to be the only determinant of the success of the procedure. In the 1990s, direct pulp caps with bonded resins adhesive were reported to yield good medium-term results [2]. However, deterioration of the material, especially the sealing junctions, had not been adequately considered. Although the results were acceptable over a period of months, destruction of the seal and subsequent infiltration of bacteria either led to acute inflammatory responses several months after treatment or to 'low-level' pulpal necrosis [3]. These shortcomings resulted in a paradigm shift in the underlying biological concepts. Complete, biological closure of the wound comprising a long-term seal came to be seen as essential. This was initially achieved through the use of materials with bioactive properties, followed by the development of other materials with the explicit goal of inducing dentin bridge formation.

For years, calcium hydroxide has been used as a capping material, either undiluted or in combination with resins for easier manipulation [4]. The best-known product of this kind is Dycal® (Dentsply, De Trey). Although the application of this material directly to the pulp results in the formation of a mineral barrier (usually wrongly named 'dentine bridge'), this barrier is neither uniform nor bonded to the dentin wall, thus precluding the formation of a long-lasting seal [5]. Since this material tends to dissolve over time, after a few months, the clinical situation is similar to that when no capping material was used for the treatment. While calcium hydroxide has been the pulp-capping material of choice for many years, this is no longer the case.

A capping material should have a number of specific features, of which the following three are crucial [6]:

- It creates an immediate protection of the exposed pulp in order to protect it in the first

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few weeks before the mineralized bridge is formed.
- It meets all non-toxicity and biocompatibility criteria.
- It has bioactive properties that trigger the biological principles involved in the formation of a mineralized barrier between the pulp being treated and the material itself.

Once the pulp has been exposed, the odontoblasts layer is usually damaged. As these cells are the only dentin-producing cells, the formation of a mineralized barrier necessitates induction of the growth of neo-odontoblasts, as the latter are the only cells that can secrete dentin. Since these highly differentiated cells are post-mitotic (and hence not renewable by mitotic cell division, as is the case for the other tissues), the healing process requires activation of regenerative mechanisms [7].

In a reparative process, progenitor cells are recruited to the wound site by chemotaxis or plithotaxis [8]. Upon coming into contact with the capping material, these cells differentiate into dentin-secreting cells and their biological functions are activated. Ideally, the biomaterial should give rise to the following three responses: chemotaxis, stimulation of differentiation, and activation of dentin synthesis. The results obtained to date with biomaterials have often been discovered by chance, once the dental device in question had become commercially available.

Dentin is a partially mineralized tissue for which the organic phase consists of a matrix of collagen I enriched with a number of non-collagen matrix proteins. These proteins are initially secreted by the odontoblasts and then fossilized during the mineralization process [9]. The multitude of matrix proteins includes a large number of growth factors, such as TGF-β, VEGF, and ADM. Any biological (carious) or therapeutic process (etching) that demineralizes dentin results in the release of these growth factors from the matrix [10]. Although most of the growth factors are eluted into the saliva, some of them are able to diffuse through the dentinal tubules and reach the dental pulp [11].

Another way to stimulate the release of growth factors from dentin is through the use of biomaterials that trigger partial but mostly controlled demineralization when it comes into contact with the dentin. The dentin matrix proteins can be released from dentin by exposure to calcium hydroxide [12], mineral trioxide aggregate [13], or any etching substance used during bonding [14]. Dentin matrix proteins boost chemotaxis, angiogenesis, and the differentiation of progenitor cells into dentinogenic cells [15]. Nevertheless, there are currently no viable therapeutic solutions available to exploit the properties of these proteins.

Odontoblasts are best known for their role in the production of dentin, both in terms of its secretion and its mineralization during primary and secondary dentinogenesis [16]. When a carious lesion occurs, dormant odontoblasts and the 'quiescent' phase of synthesis can be reactivated to synthesize tertiary dentin known as reactionary dentin [17]. Although secretion is the most described activity of odontoblasts, these cells have two other specific roles: firstly, in immunocompetence in relation with the toll-like receptors (TLRs) on their membranes that transform the binding of bacterial toxins into a cellular signal that is communicated to the underlying connective tissue [18]; and secondly, mechanosensation due to the presence of cilia on the surface of the membrane [19]. By means of these two abilities, odontoblasts act as a protective barrier for the pulp by fending off aggressors and by the production of a suitable intelligible signal for resident immune cells residing. Odontoblasts can transform information that they receive into transmissible information that can be interpreted by the underlying tissue. Odontoblasts are also particularly sensitive to growth factors and biostimulators. When dental tissue is demineralized due to caries, dentin matrix proteins are released, and they can circulate freely in the dentinal tubules [15].

2 Pulp Inflammation and Healing

Inflammation has a strong negative connotation in dentistry. Pulpitis is usually associated with pain (which is not necessary the case) and adverse

effects that lead to destroyed and necrotic pulp tissue. Treating this pain requires surgical removal of the inflamed tissue, which is often quite an invasive process and it can be difficult to determine the extent of the lesion in accordance with minimally invasive treatments. Due to the difficulties delineating the extent of the disease, the majority of cases ultimately result in a complete pulpectomy and root canal treatment.

However, despite the adverse effects of inflammation, it also has positive effects. Inflammation marks the first step of tissue healing. Inflammation helps by, on the one hand, cleaning and disinfecting the wound to be healed and, on the other hand, by triggering the secretion of a variety of substances (cytokines) that help in the healing and regeneration process [20].

In a clinical setting, pulpal inflammation is commonly referred to as being either 'reversible' or 'irreversible'. The process of inflammation either present or not and if it is, it cannot be reversed. Reversibility is considered to mean that the process is controlled well enough that it can be halted and then guided to aid in healing. When the inflammation is too advanced to be controlled, the inflammation process is said to be 'irreversible'. This term refers to a specific clinical situation associated with relatively basic diagnostic elements (the type of pain, persistence, etc.) that are poorly related to the right histo-physio-pathological status of the pulp tissue. This lack of correlation has been demonstrated for years [21] and has been confirmed with a number of experimentation multiple times [22]. Some studies have investigated markers of pulp inflammation and their potential use in diagnosis or treatment [23]. Although these markers are known to exist, more specific information remains elusive and more robust studies are needed if there are going to be reliable diagnostic tools and reproducible use cases.

Presently, without more biological information, practitioners must deal with what is currently available: information to define the patient's pain, as well as heat and electrical tests, for which the reliability is still suboptimal. More options based on observation, including controlling haemostasis at the time of pulp exposure and/or partial pulpotomy, can be used as clinical markers. Inflammation is associated with hypervascularization, which can be identified by the intensity of bleeding. Nevertheless, a similar intensity of bleeding may arise when the vascular connective tissue is cut. To visualize the difference, the pulp stump can be packed with a damp cotton pellet placed directly on the tissue, with pressure applied for 1–2 min. This is enough time to achieve haemostasis under physiological conditions. If the bleeding persists, it can be assumed that some of the pulp tissue is in fact inflamed and partial removal is necessary until healthy tissue is exposed.

As there can be considerable differences from one situation to another one, and due to the variability of interpretation from one practitioner to another one, these markers are not reliable enough to infer whether the pulp tissue is inflamed or not. Thus, it is obvious that the means for identifying and testing the presence of inflamed tissue in exposed pulp are both arbitrary and inadequate. Despite the binary classification (reversible versus irreversible), histological assessment confirms that it is not easy to differentiate one from the other.

Additional research is, therefore, necessary to identify more specific markers (biological or clinical), to develop suitable accurate diagnostic tools and to improve long-term outcomes. This is an important point to consider because being able to control inflammation remains a key factor for successful pulp capping therapies.

3 Pulp Capping and Biomaterials

Mineral trioxide aggregate (MTA) gradually became the material of choice over time as the scientific evidence of its clinical success increased [3]. Sold as a powder to be mixed with water, the substance is placed onto a glass tray and applied directly to the pulp using a dedicated instrument, such as the Micro-Apical Placement (MAP) System® (PDSA, Vevey, Switzerland). The material is not packed in, but instead is placed in direct contact with the pulp and then lightly tapped into the dentin wall using a piece of thick paper or a

cotton pellet. It is currently recommended that the way it is used for this specific circumstance is amended and that the tooth is restored immediately with bonded composite resin. Since it takes more than 4 h for the material to set, a host of precautions need to be taken because spraying water to rinse the cavity, for example could wash out the material that had just been applied. If the restoration protocol includes spraying dental tissue with water, we recommend completing this step first before application of the MTA.

The superiority of the biological properties with this material has been shown by in vitro and in vivo studies, as well as in clinical trials comparing it to the calcium hydroxide [24]. The dentin bridges formed using this material have been shown to have a better histological quality compared to those formed with calcium hydroxide (3).

One of the main drawbacks of this material is the difficulty manipulating it and the risk of inducing dyschromia of the tooth due to the presence of bismuth oxide, which is typically added to the material to improve its radiopacity. Multiple manufacturers have spent years developing a number of similar materials (hydraulic cements) with the aim to bypass this limitation, thereby resulting in the replacement of bismuth oxide with zirconium oxide.

A hydraulic tricalcium silicate–based material (Biodentine®, Septodont, Saint-Maur-des-Fosses, France) was marketed in 2012. Initially developed as a dentine substitute for coronal fillings, it exerted effects on biological tissues that led to an extension of its indications to include pulp capping [25]. One of its notable qualities is its ability to initiate mineralization [26] and cellular differentiation [25]. These results are ample reason for optimism regarding its long-term clinical use.

In addition to their ability to protect the pulp and their biological activity (inflammation control), these capping materials also have the capacity to release dentin matrix proteins from the dentin upon contact with such a material. This has been demonstrated for calcium hydroxide [12] and MTA [13] in particular. Therefore, these substances combine a direct biological effect on the pulp with an indirect effect by causing a gradual and delayed release of growth factors, including a number of anti-inflammatory entities. It may, therefore, at some stage become worthwhile to extend the application area of these materials to include the adjacent dentin walls where preparation of the cavity has made the dentin thinner. The material in contact with the dentin can extract matrix proteins, which can move through the dentinal tubules (which are quite large at this depth) and thus promote healing of the pulp [27]. This is an application where the use of Biodentine® may have real potential, as it could be used to fill an entire coronal cavity, which is not the case for MTA. However, the mechanical behaviour of the material still necessitates an additional procedure in which it is coated with a bonded composite that renders the restauration more aesthetically pleasing and that prevents the substitution material from dissolving.

4 Step-by-Step Procedures

4.1 Pulp Capping

The objective is to cap the pulp when it is exposed, with a dedicated material. The following step-by-step procedure can be used in most clinical situations.

1. Anaesthesia of the tooth is undertaken first, as for a restorative procedure. The use of a vasoconstrictor is an option, but its consequences for the rest of the treatment need to be considered (bleeding control step).
2. Placement of the rubber dam and disinfection.
3. Removal of the carious tissues and cleaning of the cavity with an excavator and ceramic burs while cooling with water. It is recommended to first remove most of the carious tissue before exposing the dental pulp.
4. When the cavity is very deep, the pulp is exposed.
5. Bleeding is controlled with a moist cotton pellet (using sterile water) placed in the cavity with gentle compression.
6. Removal of the cotton pellet and assessment of the bleeding. No other product should be used to stop the bleeding (ferric sulphate, laser, etc.).

Indeed, assessment of the haemorrhage is the only technique reliable enough to evaluate the inflammatory status of the pulp. If the pulp is not inflamed, the bleeding due to the wound can be stopped with gentle compression.

7. If the bleeding cannot be controlled, the exposed pulp should be removed with a sterile round bur (tungsten carbamide) with copious water to undertake a partial pulpotomy. The bleeding is then assessed as before. At this stage, it is important to keep in mind that assessment of the bleeding is necessary, although it remains a poor clinical tool. It is, however, the only one available until the new diagnostic tools will be developed. Another limiting factor is the use of a vasoconstrictor for anaesthesia. This alters the blood flow into the pulp, and the bleeding can hence be limited, thereby providing good control even when the pulp is inflamed.
8. The exposed pulp can be inflamed, but it is not infected. The dentin cavity can be disinfected with a 2% chlorhexidine solution left in the cavity for 2–3 min. Laser (Er:YAG) treatment is also an option. Sodium hypochlorite is not recommended as it alters the dentin structure, and it can interfere with the subsequent bonding process.
9. The capping material is placed directly in contact with the pulp using a dedicated device (MAP ONE; PDSA, Vevey, Switzerland), but it should not be plugged.
10. The cavity is filled with the same material if it is suitable for this purpose, such as Biodentine®. If the pulp is capped with MTA, the bonded restoration can be performed in the same session.
11. A post-operative X-ray is then taken, and the occlusion is checked.
12. The patient follow-up comprises both short- (1 month) and long- (6–12 months) term monitoring. The pulp sensitivity is checked by a cold test and a recall X-ray is also recommended.

See as an example of a pulp capping Figs. 1, 2, 3, 4, 5, and 6.

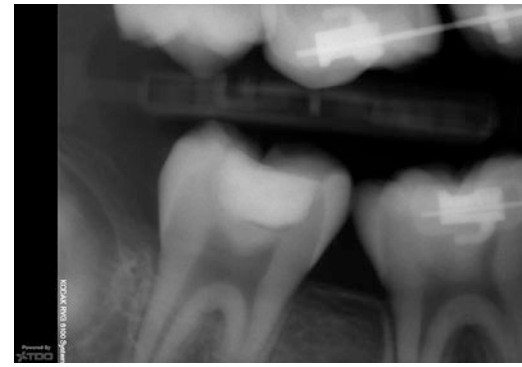

Fig. 1 Pre-operative X-ray of a 16-year-old women complaining of intermittent but acute pain. The patient was referred for root canal treatment

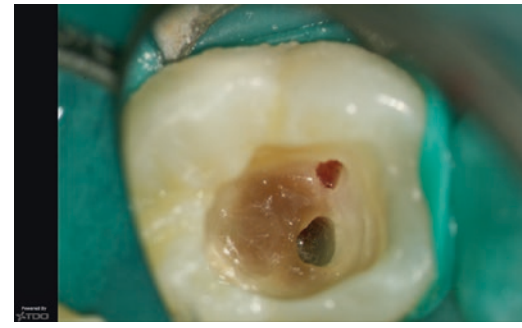

Fig. 2 After coronal restoration and carious lesion removal, two pulp horns were exposed. The buccal one was bleeding, whereas the lingual one was not. The cavity was deepened on regard to the lingual horn to remove the whole necrotic tissue and to expose vital tissue

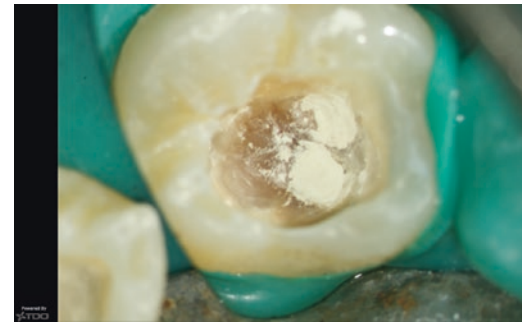

Fig. 3 Cavity was disinfected with a 2% chlorhexidine solution and pulp was capped with Mineral Trioxide Aggregate (ProRoot MTA)

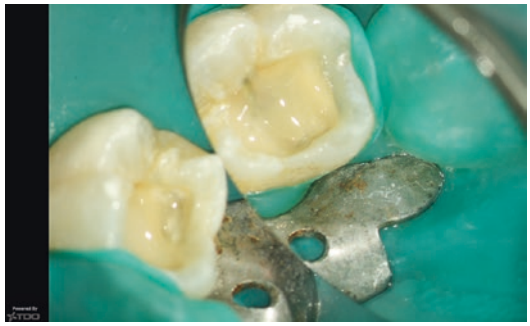

Fig. 4 The cavity was filled with a bonded composite resin in the same session. If the pulp had been capped with Biodentine®, the protocol would have been different. The cavity would have been full-filled with Biodentine® and left for 21 days. At the second visit, a new cavity would have been drilled in the material thickness and the cavity filled with bonded resin

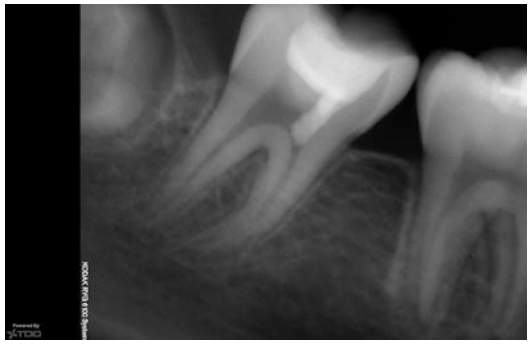

Fig. 5 The post-operative X-ray shows the deep placement of the material inside the pulp chamber

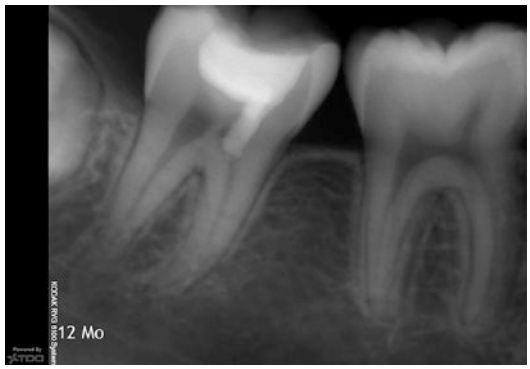

Fig. 6 Twelve Months recall X-Ray. The presence of a mineralized tissue on the close contact of MTA is clearly visible. The positive response to sensitivity tests associated to the X-ray images at 12 months postoperation leads to consider this treatment as effective with a clinical success

4.2 Pulp Chamber Pulpotomy

The clinical procedure is similar. A pulp chamber pulpotomy is indicated when the assessment of the bleeding of the pulp exposure site is not possible or in case of any doubt regarding the inflammatory status of the pulp. In such cases, it is probably safer to undertake a deep pulpotomy. The first six steps of the pulp capping remain the same, as mentioned before.

1. The pulp chamber is emptied of the entire coronal pulp with a carbamide bur used with a low-speed handpiece with copious water cooling.
2. The pulp is cut with a sharp and sterile excavator at the entrance of the root canal.
3. The bleeding is controlled by gentle pressure with a moist cotton pellet.
4. The radicular pulp stumps are capped with the capping material, as described previously.
5. The rest of the coronal cavity is then filled with the same material (Biodentine) or with a bonded composite resin.
6. A post-operative X-ray is taken to assess the quality of treatment and to check the occlusion.
7. The patient should return for short- and long-term check-ups. Note that in case of a pulp chamber pulpotomy, the sensitivity tests are not reliable.

See as a clinical example of a pulp chamber pulpotomy Figs. 7, 8, 9, 10, 11, 12, 13, and 14.

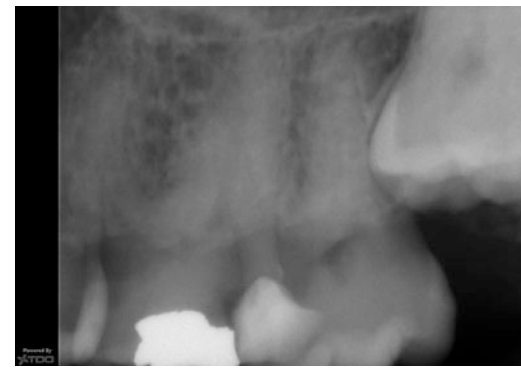

Fig. 7 Pre-operative X-ray of an upper first molar referred for a root canal treatment by his general practitioner, who placed a temporary restoration as an emergency treatment

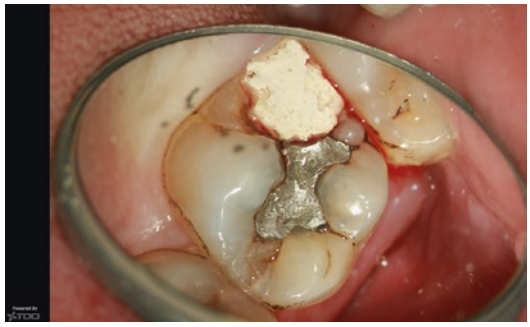

Fig. 8 Occlusal view of the crown before treatment

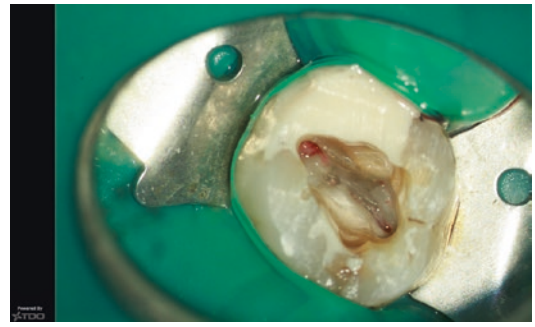

Fig. 11 A conventional access cavity was done, and the coronal pulp was removed. Haemostasis of the radicular pulp was controlled by a gentle pressure in the tissues with a sterile moist cotton pellet

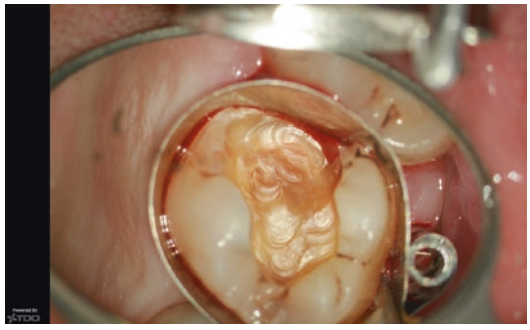

Fig. 9 The full coronal restorative material was removed

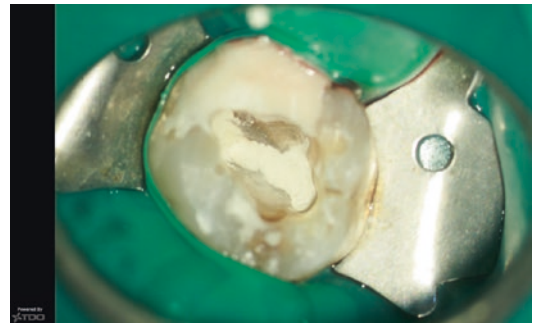

Fig. 12 Radicular pulp was capped with Mineral Trioxide Aggregate. The tooth was restored in the same session with a bonded composite resin

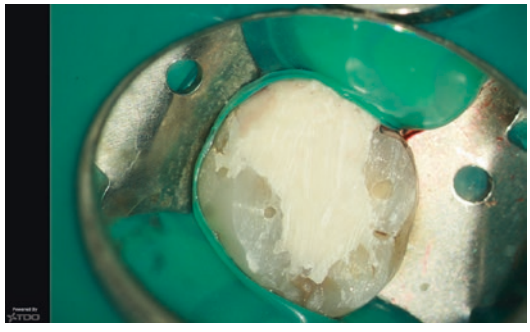

Fig. 10 The tooth is prepared exactly as for a root canal treatment. Pre-treatment restoration with a temporary restorative material (Glass Ionomer)

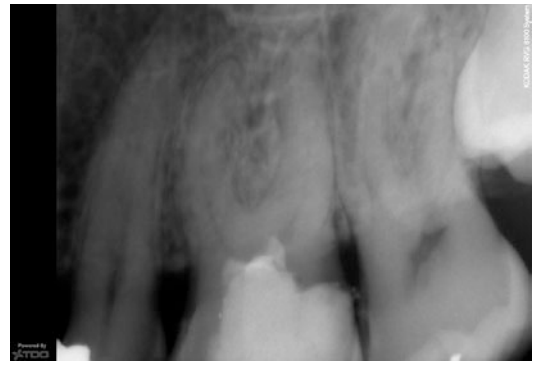

Fig. 13 Post-operative X-ray

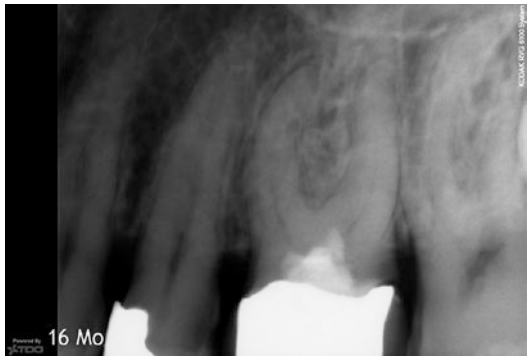

Fig. 14 The 16 months recall do not show any sign of endodontic failure. Nevertheless, the impossibility to test the pulp sensibility remains a limiting factor to conclude as a true clinical success

5 Application of Pulp Capping and 'Bioproducts' to Stimulate Regeneration

The extracellular matrix (ECM) of dentin contains a variety of molecules involved in the regulation of dentinogenesis. Attempts have been made to use ECM proteins (expressed in recombinant bacteria) to stimulate pulp regeneration [28]. The biological effects of several other ECM molecules have also been examined, including dentonin, an acidic synthetic peptide derived from matrix extracellular phosphoglycoprotein (MEPE), and A + 4 and A − 4, two splice products of the amelogenin gene. Each entity induced regeneration of superficial pulp [29].

Such biological approaches have helped to elucidate what takes place during pulp capping and regeneration. However, before they are applied clinically, more studies are needed to confirm the advantages and the safety of such bioproducts versus mineral hydraulic cements.

6 Short- and Long-Term Future Developments

Progress in the development of capping biomaterials in the past 10 years has helped restimulate interest in techniques to preserve pulp vitality. Our understanding of pulp biology continues to progress, thereby making it possible to explain the reason for certain failures because the 'Achilles heel' of these procedures remains assessment of the inflammatory state of the pulp in need of treatment. Clinically, it remains difficult to exactly know how deep down the pulp tissue needs to be removed in order to eliminate the risk of leaving any inflamed tissue. A suggestion derived from this idea was recently made in which a larger portion of the pulp is removed, thus ensuring that all of the inflamed tissue is eliminated, albeit without resulting in a complete pulpectomy of the tooth.

Until now, this treatment was restricted to primary teeth or certain immature teeth. However, in coming years, pulp chamber pulpotomies may come to be seen as an endodontic therapeutic alternative to pulpectomies and root canal treatments. In this procedure, all of the pulp chamber tissue is removed, and the radicular stumps are covered with a capping material. Preliminary studies have yielded promising results [30], although these need to be substantiated by more formal studies before this can become a generally viable procedure.

7 Conclusions

The aim of any endodontic treatment is to prevent bacterial leakage from the mouth (which contains commensal flora) to the underlying maxillary or mandibular bone, which is free of any infection and must be protected from any bacterial contamination. Based on this postulate, every clinical process that allows bacteria progression to be blocked warrants being considered.

Pulp capping and pulp chamber pulpotomy allow bacterial penetration to be prevented, merely by placing a material in direct contact with the pulp tissue. This material ensures sealing of the lesion in just a few minutes/hours and it has a double protective effect by induction of the formation of a mineralized barrier between the material and the pulp tissue. Thus, partial and full chamber pulpotomies, followed by pulp capping, should be considered to be minimally invasive endodontic treatments. Furthermore, new strategies involving coronal restoration with bonded composite resins, or bonded prosthetic

restoration, now allow minimization of the indications for the root canal treatments, at least for restorative reasons.

References

1. Simon S, Smith AJ. Regenerative endodontics. Br Dent J. 2014;216:E13.
2. Cox CF, Hafez AA, Akimoto N, Otsuki M, Suzuki S, Tarim B. Biocompatibility of primer, adhesive and resin composite systems on non-exposed and exposed pulps of non-human primate teeth. Am J Dent. 1998;11 Spec No:S55–63.
3. Nair PN, Duncan HF, Pitt Ford TR, Luder HU. Histological, ultrastructural and quantitative investigations on the response of healthy human pulps to experimental capping with mineral trioxide aggregate: a randomized controlled trial. Int Endod J. 2008;41:128–50.
4. Heys DR, Cox CF, Heys RJ, Avery JK. Histological considerations of direct pulp capping agents. J Dent Res. 1981;60:1371–9.
5. Goldberg F, Massone EJ, Spielberg C. Evaluation of the dentinal bridge after pulpotomy and calcium hydroxide dressing. J Endod. 1984;10:318–20.
6. Witherspoon DE. Vital pulp therapy with new materials: new directions and treatment perspectives--permanent teeth. J Endod. 2008;34:S25–8.
7. Simon S, Cooper P, Isaac J, Berdal A. Tissue engineering and endodontics. In: Preprosthetic and maxillofacial surgery: biomaterials, bone grafting and tissue engineering. Cambridge: Woodhead Publishing Limited; 2011.
8. Hirata A, Dimitrova-Nakov S, Djole S-X, Ardila H, Baudry A, Kellermann O, et al. Plithotaxis, a collective cell migration, regulates the sliding of proliferating pulp cells located in the apical niche. Connect Tissue Res. 2014;55(Suppl 1):68–72.
9. Smith AJ, Duncan HF, Diogenes A, Simon S, Cooper PR. Exploiting the bioactive properties of the dentin-pulp complex in regenerative endodontics. J Endod. 2016;42:47–56.
10. Simon SRJ, Berdal A, Cooper PR, Lumley PJ, Tomson PL, Smith AJ. Dentin-pulp complex regeneration: from lab to clinic. Adv Dent Res. 2011;23:340–5.
11. Sloan AJ, Shelton RM, Hann AC, Moxham BJ, Smith AJ. An in vitro approach for the study of dentinogenesis by organ culture of the dentine-pulp complex from rat incisor teeth. Arch Oral Biol. 1998;43:421–30.
12. Graham L, Cooper PR, Cassidy N, Nor JE, Sloan AJ, Smith AJ. The effect of calcium hydroxide on solubilisation of bio-active dentine matrix components. Biomaterials. 2006;27:2865–73.
13. Tomson PL, Grover LM, Lumley PJ, Sloan AJ, Smith AJ, Cooper PR. Dissolution of bio-active dentine matrix components by mineral trioxide aggregate. J Dent. 2007;35:636–42.
14. Ferracane JL, Cooper PR, Smith AJ. Can interaction of materials with the dentin-pulp complex contribute to dentin regeneration? Odontology. 2010;98:2–14.
15. Liu J, Jin T, Ritchie H, Smith A, Clarkson B. In vitro differentiation and mineralization of human dental pulp cells induced by dentin extract. In Vitro Cell Dev Biol Anim. 2005;41:232.
16. Simon SR, Smith AJ, Lumley PJ, Berdal A, Smith G, Finney S, et al. Molecular characterisation of young and mature odontoblasts. Bone. 2009;45:693–703.
17. Simon S, Cooper PR, Lumley PJ, Berdal A, Tomson PL, Smith AJ. Understanding pulp biology for routine clinical practice. Endod Pract Today. 2009;3:171–84.
18. Farges JC, Keller JF, Carrouel F, Durand SH, Romeas A, Bleicher F, et al. Odontoblasts in the dental pulp immune response. J Exp Zool B Mol Dev Evol. 2009;312B:425–36.
19. Magloire H, Couble ML, Thivichon-Prince B, Maurin JC, Bleicher F. Odontoblast: a mechano-sensory cell. J Exp Zool B Mol Dev Evol. 2008;312B:416.
20. Cooper PR, Takahashi Y, Graham LW, Simon S, Imazato S, Smith AJ. Inflammation-regeneration interplay in the dentine-pulp complex. J Dent. 2010;38:687.
21. Dummer PM, Hicks R, Huws D. Clinical signs and symptoms in pulp disease. Int Endod J. 1980;13:27–35.
22. Ricucci D, Loghin S, Siqueira JF. Correlation between clinical and histologic pulp diagnoses. J Endod. 2014;40:1932–9.
23. Zanini M, Meyer E, Simon S. Pulp inflammation diagnosis from clinical to inflammatory mediators: a systematic review. J Endod. 2017;43:1033.
24. Hilton TJ, Ferracane JL, Mancl L. Comparison of CaOH with MTA for direct pulp capping: a PBRN randomized clinical trial. J Dent Res. 2013;92:16S–22S.
25. Zanini M, Sautier JM, Berdal A, Simon S. Biodentine induces immortalized murine pulp cell differentiation into odontoblast-like cells and stimulates biomineralization. J Endod. 2012;38:1220–6.
26. Laurent P, Camps J, About I. Biodentine(TM) induces TGF-β1 release from human pulp cells and early dental pulp mineralization. Int Endod J. 2012;45:439.
27. Simon SR, Smith AJ, Lumley PJ, Cooper PR, Berdal A. The pulp healing process: from generation to regeneration. Endod Top. 2012;26:41–56.
28. Rutherford RB, Spångberg L, Tucker M, Rueger D, Charette M. The time-course of the induction of reparative dentine formation in monkeys by recombinant human osteogenic protein-1. Arch Oral Biol. 1994;39:833–8.
29. Goldberg M, Six N, Chaussain C, DenBesten P, Veis A, Poliard A. Dentin extracellular matrix molecules implanted into exposed pulps generate reparative dentin: a novel strategy in regenerative dentistry. J Dent Res. 2009;88:396–9.
30. Simon S, Perard M, Zanini M, Smith AJ, Charpentier E, Djole SX, et al. Should pulp chamber pulpotomy be seen as a permanent treatment? Some preliminary thoughts. Int Endod J. 2013;46:79–87.