Minimally invasive endodontics a new diagnostic system for assessing pulpitis and subsequent treatment needs

Wolters, W. J., Duncan, H. F., Tomson, P. L., Karim, E. I., McKenna, G., Dorri, M., ... van der Sluis, L. W. M. (2017). Minimally invasive endodontics a new diagnostic system for assessing pulpitis and subsequent treatment needs. International Endodontic Journal, 50(9), 825-829. https://doi.org/10.1111/iej.12793

Published in:
International Endodontic Journal

Document Version:
Peer reviewed version

Queen's University Belfast - Research Portal:
Link to publication record in Queen's University Belfast Research Portal

Minimally invasive endodontics -

A new diagnostic system for assessing pulpitis and subsequent treatment needs

W.J. Wolters, H.F. Duncan, P. L. Tomson, I.A. El Karim, G. McKenna, M.Dorri, L. Stangvaltaite, L.W.M. van der Sluis.

W.J. Wolters

Center of Dentistry and Oral Hygiene

University medical Center Groningen

Antonius Deusinglaan 1

9713 AV Groningen

the Netherlands

w.j.wolters@umcg.nl

H.F.Duncan

Division of Restorative Dentistry & Periodontology

Dublin Dental University Hospital

Trinity College Dublin

Lincoln Place

Dublin 2

Ireland

P. L. Tomson

Senior Clinical Lecturer and Honorary Consultant in Restorative Dentistry

College of Medical & Dental Sciences

The University of Birmingham School of Dentistry

5 Mill Pool Way

Edgbaston

Birmingham B5 7EG

UK

I.A. El Karim

Senior Lecturer and Consultant in Restorative Dentistry

Centre for Dentistry

School of Medicine, Dentistry and Biomedical Sciences

Queen's University Belfast

Grosvenor Road, Belfast BT12 6BP

G. McKenna

Senior Lecturer / Consultant in Restorative Dentistry,

Centre for Public Health,

Queens University Belfast,

Institute of Clinical Sciences Block B,

Grosvenor Road,

Belfast,

BT12 6BJ.

M.Dorri

Clinical Lecturer in Restorative Dentistry

School of Oral and Dental Sciences,

Bristol Dental School,

Lower Maudlin Street,

Bristol BS1 2LY

L. Stangvaltaite

Department of Clinical Dentistry

Faculty of Health Sciences

UiT The Arctic University of Norway

NO-9037 Tromsø, Norway

L. van der Sluis,

Center of Dentistry and Oral Hygiene

University medical Center Groningen

Antonius Deusinglaan 1

9713 AV Groningen

the Netherlands

Abstract

Developments in our understanding of pulp biology and the response of the pulp to the release of dentine-bound bioactive growth factors have highlighted that the pulp in mature teeth has a greater regenerative capacity than previously thought. Preserving all or part of the pulp is beneficial as it is less invasive than conventional root canal treatment. It retains the biological immune response and could help prevent infection of the periapical tissues. Recent correlations between histological findings and corresponding clinical signs, symptoms and tests can be used to carefully differentiate between different stages of reversible and irreversible pulpitis. In addition, it has become evident that if the correct vital pulp treatment is employed, pulp tissue previously diagnosed as irreversibly inflamed can at least be partially maintained. This highlights a problem with the existing diagnostic classification system in that the use of the term “irreversible” is misleading. Therefore, the aim of this communication is to both introduce a new way of diagnosing the various stages of pulpitis and also to relate the diagnosis to alternative minimal invasive treatment choices based on the degree of pulpal inflammation.

Aim:

To introduce a new way of thinking about the inflamed pulp. We want to highlight that there is reversibly inflamed tissue in pulps that are currently diagnosed as irreversibly inflamed. This implies that the currently employed terminology may not reflect the actual inflammatory status of pulps evaluated clinically. We therefore propose and introduce a new diagnostic system with new terminology to highlight the healing potential of the pulp. This also implies that current treatment strategies are evaluated and revised to maintain pulp vitality with associated benefits.

Introduction

In the majority of cases of mature teeth diagnosed with pulpitis or apical periodontitis root canal treatment is the therapy of choice in order to save the tooth. Inherent in this procedure is loss of dental hard tissue and subsequent weakening of the treated tooth, (Kishen 2006, Al-Omiri *et al.* 2010) making them more prone to fracture (Reeh *et al*. 1989, Al-Omiri *et al.* 2010). Apical periodontitis indicates a dental infectious disease related to the presence of microorganisms in and outside the root canal system (Haapasalo *et al.* 2011). To resolve apical periodontitis the conventional treatment is a root canal treatment procedure with the aim to reduce the number of bacteria in the root canal system that cause infection to such a degree that there is resolution of the apical lesion, however, this is challenging. During the past 30 years the considerable improvement of the technical aspects of the endodontic treatment, new and highly advanced equipment and materials have not resulted in improved success rates globally (Kirkevang *et al.* 2001, Dugas *et al.* 2003, Georgopoulou *et al.* 2005, Wu *et al.* 2009, Peters *et al.* 2011, López-López *et al.* 2012). A Swedish study has shown that improvement of the radiographic quality of the root canal filling performed by general practitioners, having attended an intensive training program on root canal therapy, did not result in better clinical success rates (Koch *et al.* 2014). Moreover, the research has shown that infected root canals do not become predictably sterile with conventional treatments (McGurkin-Smith *et al.* 2005). It has to be realized that an infected root canal system cannot be disinfected completely because of the complex structure of dentine and the anatomy of the root canal system with its isthmuses and oval shaped canals (Nair *et al.* 2005). In addition, rapid bacterial growth and biofilm formation make mechanical and chemical removal difficult (Siqueira 2001, Martinho *et al.* 2008). Cross-sectional research has shown that around forty percent of endodontically treated teeth are associated with an apical radiolucency when examined using dental radiographs (Peters *et al.* 2011), indicating failure of the procedure, as only a small proportion of apical radiolucencies remain visible as fibrotic healing scars (Nair *et al.* 1999, Love & Firth 2009). Furthermore, endodontically treated teeth without visible radiographic signs of apical periodontitis

can still be infected (Molander *et al.* 1998, Riccuci *et al.* 2014). A diagnosis of apical periodontitis based on dental radiographs is inaccurate (Bender & Selzer 1961, de Paula Silva *et al.* 2009), with approximately, forty percent of lesions associated with apical periodontitis are not detected using conventional dental radiograph techniques (Wu *et al*. 2009). Therefore, the actual failure rate of standard endodontic treatments is significantly higher and it can be concluded that conventional root canal treatment carried out in practice does not have a high success rate. Furthermore, these treatments are lengthy and costly and are often subject to retreatment (Figdor 2002). In summary, this means that conventional root canal treatments are less effective than expected with a high probability of failure at a large cost to society.

It is evident that less invasive alternative solutions are required to improve the success of endodontic procedures beyond the improvement of the 'tools and gadgets' used during conventional root canal treatment. New insights in pulp biology have been gained and recent clinical research on vital pulp therapy now provide options for developing new biologically-driven treatment protocols(Aguilar *et al.* 2011, Simon *et al.* 2013, Tomson *et al.* 2016). Such treatment modalities have two huge advantages: firstly, pulp tissue is preserved, thus maintaining its physiological and defensive functions; secondly, less hard tooth tissue will be removed which results in less weakening of the tooth. Combining knowledge of pulp biology with insight into why conventional therapies often fail stimulates a shift in thinking about endodontic treatment. Avoiding full pulpectomies (complete removal of the pulp to the apical constriction), where possible, could be the first step in improving treatment outcomes. A biological immune response from even a partially retained pulp could improve the treatment outcome by preventing infection of the apical area (Aguilar *et al.* 2011).

Dentine as a bioactive substance

With increasing knowledge regarding the biological healing processes in response to infected carious dentine and pulp a new understanding of vital pulpal therapy emerges (Simon *et al.* 2011). Dentine is a vital, cellular tissue, containing the cellular processes of the odontoblasts that lay in the pulp.

Therefore dentine and pulp must be considered together as a pulpo-dentinal complex (Pashley 1996). Recent research shows that the pulp is more resilient to significant microbial attacks than previously thought (Farges *et al*. 2013, Bjørndal *et al.* 2014, Cooper *et al.* 2014). Pulpal defense mechanisms to reduce the diffusion of microbes and microbial products towards the pulp include sclerosis of dentinal tubules and the formation of tertiary dentin (Bjørndal 2008). Apart from sclerosis and the replacement of dead odontoblasts, a host of growth factors including TGF-β, ADM, IGF-1 /-2 are released from the pulpo-dentinal complex when dentine is demineralized during the progression of a carious lesion (Finkelman *et al.* 1990, Cassidy *et al.* 1997, Cooper *et al.* 2010, Cooper *et al*. 2011). These growth factors can have a positive effect on the pulpal response by enhancing the processes involved in pulp repair and regeneration (Smith *et al.* 2012, Smith *et al.* 2016). Ongoing research shows the impact of different growth factors encapsulated in dentin (Tomson *et al.* 2016). The fact that the regenerative potential of the pulpo-dentinal complex is evident in teeth with symptoms indicative of irreversible pulpitis indicates that current classification of pulpitis may need to be revised (Ricucci *et al.* 2014). Probably cases traditionally deemed irreversible may in fact still be salvageable, thereby shifting the balance of what was irreversible towards reversible, when the correct treatment is applied (Ricucci *et al.* 2014, Taha *et al.* 2015).

Minimally invasive endodontics- Endolight

Traditionally it was thought that there is a poor relationship between clinical signs and symptoms and the histological state of the pulp in mature teeth (Selzer & Bender 1963, Garfunkel *et al.* 1973, Dummer *et al*. 1980), however, recently this was questioned (Ricucci *et al*. 2014). This histological study showed that there is good correlation between clinical symptoms of pulpitis and the corresponding histological state of a diseased pulp. In cases with IP the morphological changes indicating inflammation or necrosis were principally occurring in the coronal pulp whilst the radicular pulp was viable. This suggests that the radicular pulp could potentially be retained with a pulpotomy

procedure , thus preventing the need for a pulpectomy. Such a treatment philosophy could have the following advantages:

1. preservation of immunological functions and retaining structural integrity of the tooth.

2. simplifying treatment procedures and avoiding treatment complications associated with difficult root canal anatomy.

3. reducing cost and inconvenience for patients and society.

The success of vital pulp therapy depends on proper case selection and appropriate treatment protocols (Taha *et al.* 2015). Teeth exhibiting symptoms suggestive of irreversible pulpitis have little chance to revert to normal if no other intervention takes place than removal of irritants. In these cases the section of the pulp which is inflamed must be removed so that the remaining uninflamed tissue can recover and heal (Ricucci *et al.* 2014).

If with the proper intervention, extensively inflamed pulps can be maintained this then begs the questions, should the term "irreversible" be used in our diagnostic criteria? As such a term condems the pulp with a resulting treatment of pulpectomy or tooth extraction. Therefore as long as there is some uninflamed pulp tissue and the complete pulp has not become necrotic, this uninflamed vital tissue can be managed and retained. Such an approach would carry the advantages of those discussed above. The authors propose a new diagnostic system of pulpitis and associated treatment options for how the inflamed pulp should be managed.

A new treatment philosophy 'Endo-Light'

In light of the information of the above mentioned recent studies, it becomes clear that it is time for traditional thinking and conventional root canal treatment procedures to be revisited. Probably, many pulps diagnosed with irreversible pulpitis have the potential to heal after implementing the appropriate minimally invasive or 'light' treatments corresponding to their clinical revised diagnosis.

This means that lingering pain after a stimulus, normally recognized as indicative for irreversible pulpitits, may not necessarily correspond to an irreversible state of inflammation of part or the complete pulp. It appears that only the pulp tissue located in the pulp chamber is irreversibly inflamed (presenting prolonged lingering pain after cold/hot stimulus) and therefore indirect pulp treatment (IPT) or coronal pulpotomy (Asgary *et al.* 2014) could be an excellent alternative of less invasive treatment which allows uninflamed tissue in place to heal and regenerate.

A recent positive development in pulpal diagnosis was introduction of new classification based on clinical symptoms (Hashem eta l 2015) .

Hashem and co-workers classified pulpitis as:

= **mild reversible pulpitis**: patients' descriptions of sensitivity to hot, cold, and sweet lasting up to 15 to 20 s and settling spontaneously

= **severe reversible pulpitis**: increased pain for more than several minutes and needing oral

= **irreversible pulpitis**: persistent dull throbbing pain, sharp spontaneous pain, tenderness to percussion or pain exacerbated by lying down.

We propose to change the criteria for the clinical diagnosis of (ir)reversible pulpitis and suggest expansion of the diagnostic classification of pulpal inflammation and relate the diagnosis to minimally invasive treatments, whereby the extensively inflamed tissue is removed and leaving uninflamed tissue in place. This means that there is always vital pulp tissue that has the potential to heal if it is managed correctly.

Our proposal for new clinical pulp diagnosis terminology and associated treatment modalities

1. *Initial Pulpitis*

Heightened but not lengthened response to the cold test, not sensitive upon percussion and no spontaneous pain.

Formatted: Justified

Therapy: removal of the stimulus

2. *Mild Pulpitis*

Heightened and lengthened reaction to cold, warmth and sweet stimuli that can last up to 20 seconds but then subsides, possibly percussion sensitive and spontaneous dull pain that can be suppressed with pain medication if required. According to the histological situation that fits these findings it would be implied that there is limited local inflammation confined to the crown pulp.

Therapy: IPT or removal of the stimulus (van der Sluis *et al.* 2013, Asgary et al. 2014)

3. *Moderate Pulpitis*

Clear symptoms, strong, heightened and prolonged reaction to cold, which can last for minutes, possibly percussion sensitive and spontaneous dull pain that can be more or less suppressed with pain medication. According to the histological situation that fits these findings it would be implied that there is extensive local inflammation confined to the crown pulp.

Therapy: Coronal pulpotomy – partly/completely or removal of the stimulus

4. *Severe Pulpitis*

Strong pain sensation, pain medication does not give much relief, clear pain reaction to warmth, sharp to dull pain, and the patient does not sleep anymore because of the pain (gets worse when lying down). Tooth is very sensitive to touch and percussion. According to the histological situation that fits these findings it would be implied that there is extensive local inflammation in the crown pulp that possibly extends into the root canals.

Therapy: Coronal pulpotomy- if there is no prolonged bleeding of pulp stumps in the orifices of the canals these will be covered with MTA in mature teeth, followed by restoration. If one or more of the pulp stumps keeps bleeding after rinsing with 2ml NaOCl 2% a short pulpotomy can be carried out whereby more inflamed tissue is removed from the canal till about 3-4mm from the roentgenologic

apex. If bleeding ceases then the vital short stumps is plugged with gutta percha and cement at this working length. If bleeding persists a full pulpectomy needs to be performed in order to remove all inflamed tissue from the canal (Matsuo *et al.* 1996).

5. *Total pulp necrosis*

No reaction to the cold test. May be painful upon percussion. Patient may have had an episode of pain in the past. Radiographic signs indicative of inflammation may be visible on an x ray.

Therapy: Pulpectomy and conventional root canal treatment

Recapitulating: 'Endo-Light', the minimal invasive endodontic approach' can benefit dental health care on several aspects:

= maintaining the viability of the pulp as long as possible to induce a biological response to prevent apical periodontitis and improving the success rate of vital pulp treatment
= saving tooth structure and consequently increasing tooth survival
= saving time and cost for both the patient and/or society
= reducing pain and discomfort for the patient with these less invasive treatments and keeping teeth longer functional

If endodontic treatment fails the following alternatives can be considered: endodontic retreatment, apical surgery or extraction.

Conclusion

Vital pulp treatment has been shown to be highly successful if the intervention has been performed with the accompanying clinical symptoms as a guideline. There is good correlation between clinical symptoms of pulpitis and the corresponding histological state of an inflamed pulp. This information with the pretreatment and mid operative clinical findings can be used to potentially save and retain pulp and tooth tissue with associated benefits. Developments in our understanding of pulp biology

and the response of the pulp to the release of dentine-bound bioactive growth factors has made it clear that the pulp has substantial regenerative capabilities and that inflammation is a normal part of the healing response of the pulp. A diseased pulp, even if it is in an inflamed state, can heal if most of the inflamed/necrotic tissue is removed. This gives the remaining tissue a chance to heal because vital pulp tissue that has been managed properly is quite resilient. Preserving all or part of the pulp is beneficial as it is less invasive than conventional root canal treatment. It saves tooth structure and consequently increases tooth survival. It saves time and cost for both the patient and/or society and reduces pain and discomfort for the patient. It keeps teeth longer functional and retains the biological immune response, thereby preventing infection of the periapical tissues. The authors hope that with the proposition of a new system for diagnosing different stages of pulpitis, using associated symptoms and implementing new minimally invasive treatment strategies, new debate and research in the area of vital pulp treatment will be stimulated with improvement in treatment results for patients in the future.

The proposed changes based mostly on in vitro pulp biology studies and that of Ricucci et al. To properly ascertain the potential of these treatment protocols, clinical studies for validation of these procedures are needed. In order to do so the authors of this editorial are currently working to set up an international network to carry out research using this diagnostic system and these treatment options with subsequent evaluation of the outcome.

References

Aguilar P, Linsuwanont P (2011) Vital pulp therapy in vital permanent teeth with cariously exposed pulp: a systematic review. *Journal of Endodontics* **5**, 581–7.

Al-Omiri MK, Mahmoud AA, Rayyan MR, Abu-Hammad O (2010) Fracture resistance of teeth restored with post-retained restorations: an overview. *Journal of Endodontics* **9**, 1439-49.

Alqaderi H, Lee CT, Borzangy S, Pagonis TC (2016) Coronal pulpotomy for cariously exposed permanent posterior teeth with closed apices: A systematic review and meta-analysis. *Journal of Dentistry* **44**, 1-7.

Alqaderi HE, Al-Mutawa SA, Qudeimat MA (2014) MTA pulpotomy as an alternative to root canal treatment in children's permanent teeth in a dental public health setting. *Journal of Dentistry* **11**, 1390–5.

Asgary S, Fazlyab M, Sabbagh S, Eghbal MJ (2014) Outcomes of different vital pulp therapy techniques on symptomatic permanent teeth : a case series. *Iranian Endodontic Journal* **4**, 295-300.

Bender IB, Seltzer S (1961) Roentgenographic and direct observation of experimental lesions in bone: I. *The Journal of the American Dental Association* **62**, 152–60.

Bjørndal L (2008) The Caries Process and Its Effect on the Pulp: The Science Is Changing and So Is Our Understanding. *Journal of Endodontics* **7**, S2-S5.

Bjørndal L, Demant S, Dabelsteen S (2014) Depth and activity of carious lesions as indicators for the regenerative potential of dental pulp after intervention. *Journal of Endodontics* **40**, S76-81.

Cassidy N, Fahey M, Prime SS, Smith AJ (1997) Comparative analysis of transforming growth factor-β isoforms 1–3 in human and rabbit dentine. *Archives of Oral Biology* **3**, 219-23.

Cooper PR, Holder MJ, Smith AJ (2014) Inflammation and regeneration in the dentin-pulp complex: a double-edged sword. *Journal of Endodontics* **40**, S46-51.

Cooper PR, McLachlan JL, Simon S, Graham LW, Smith AJ (2011) Mediators of inflammation and regeneration. *Advances in Dental Research* **3**, 290-5.

Cooper PR, Takahashi Y, Graham LW, Simon S, Imazato S, Smith AJ (2010) Inflammation-regeneration interplay in the dentine-pulp complex. *Journal of Dentistry* **9**, 687-97.

De Paula-Silva FW, Wu MK, Leonardo MR, da Silva LA, Wesselink PR (2009) Accuracy of periapical radiography and cone-beam computed tomography scans in diagnosing apical periodontitis using histopathological findings as a gold standard. *Journal of Endodontics* **7**, 1009-12.

Dugas NN~~1~~, Lawrence HP, Teplitsky PE, Pharoah MJ, Friedman S (2003) Periapical health and treatment quality assessment of root-filled teeth in two Canadian populations. *International Endodontic Journal* **3**, 181-92.

Dummer PM, Hicks R, Huws D (1980) Clinical signs and symptoms in pulp disease. *International Endodontic Journal* **1**, 27-35.

Farges JC, Alliot-Licht B, Baudouin C, Msika P, Bleicher F, Carrouel F (2013) Odontoblast control of dental pulp inflammation triggered by cariogenic bacteria. *Frontiers in Physiology* **4**, article 326.

Figdor D (2002) Apical periodontitis: a very prevalent problem. *Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology, and Endodontology* **6**, 651–2.

Finkelman RD, Mohan S, Jennings JC, Taylor AK, Jepsen S, Baylink DJ (1990) Quantitation of growth factors IGF-I, SGF/IGF-II, and TGF-β in human dentin. *Journal of Bone and Mineral Research* **7**, 717-23.

Garfunkel A, Sela J, Ulmansky M (1973) Dental pulp pathosis. Clinicopathologic correlations based on 109 cases. *Oral Surgery, Oral Medicine, Oral Pathology* **1**, 110-7.

Georgopoulou MK1, Spanaki-Voreadi AP, Pantazis N, Kontakiotis EG (2005) Frequency and distribution of root filled teeth and apical periodontitis in a Greek population. *International Endodontic Journal* **2**, 105-11.

Haapasalo M, Shen Y, Ricucci D (2011) Reasons for persistent and emerging post-treatment endodontic disease. *Endodontic Topics* **18**, 31-50.

Hashem D, Mannocci F, Patel S, Manoharan A, Brown JE, Watson TE, Banerjee (2015) A Clinical and Radiographic Assessment of the Efficacy of Calcium Silicate Indirect Pulp Capping: A Randomized Controlled Clinical Trial. *Journal of Dental Research* **94**, 562-8.

Kirkevang LL~~1~~, Hörsted-Bindslev P, Ørstavik D, Wenzel A (2001) Frequency and distribution of endodontically treated teeth and apical periodontitis in an urban Danish population. *International Endodontic Journal* **3**, 189-205.

Kishen A. (2006), Mechanisms and risk factors for fracture predilection in endodontically treated teeth. *Endodontic Topics* **13**, 57–83

Koch M, Wolf E, Tegelberg A, Petersson K (2014) Effect of education intervention on the quality and long-term outcomes of root canal treatment in general practice. *International Endodontic Journal* **7**, 680-9.

López-López J, Jané-Salas E, Estrugo-Devesa A, Castellanos-Cosano L, Martín-González J, Velasco-Ortega E, Segura-Egea JJ (2012) Frequency and distribution of root-filled teeth and apical periodontitis in an adult population of Barcelona, Spain. *International Dental Journal* **1**, 40-6.

Love RM, Firth N (2009) Histopathological profile of surgically removed persistent periapical radiolucent lesions of endodontic origin. *International Endodontic Journal* **3**, 198–202.

Martinho FC~~1~~, Gomes BP (2008) Quantification of endotoxins and cultivable bacteria in root canal infection before and after chemomechanical preparation with 2.5% sodium hypochlorite. *Journal of Endodontics* **3**, 268-72.

Matsuo T, Nakanishi T, Shimizu H, Ebisu S (1996) A clinical study of direct pulp capping applied to carious-exposed pulps. *Journal of Endodontics* **10**, 551-6.

McGurkin-Smith R, Trope M, Caplan D, Sigurdsson A (2005) Reduction of intracanal bacteria using GT rotary instrumentation, 5.25% NaOCl, EDTA, and Ca(OH)2. *Journal of Endodontics* **5**, 359-63.

Molander A, Reit C, Dahlén G, Kvist T (1998) Microbiological status of root-filled teeth with apical periodontitis. *International Endodontic Journal* **1**, 1-7.

Nair PN, Henry S, Cano V, Vera J(2005) Microbial status of apical root canal system of human mandibular first molars with primary apical periodontitis after "one-visit" endodontic treatment. *Oral surgery, Oral medicine, Oral pathology, Oral radiology and Endododontics* **2**, 231-52.

Nair PN, Sjögren U, Figdor D, Sundqvist G (1999) Persistent periapical radiolucencies of root-filled human teeth, failed endodontic treatments, and periapical scars. *Oral surgery, Oral medicine, Oral pathology, Oral radiology and Endododontics* **5**, 617-27.

Pashley DH (1996) Dynamics of the pulpo-dentin complex. *Critical Reviews in Oral Biology & Medicine* **2**, 104-33.

Peters LB, Lindeboom JA, Elst ME, Wesselink PR (2011) Prevalence of apical periodontitis relative to endodontic treatment in an adult Dutch population: a repeated cross-sectional study. *Oral surgery, Oral medicine, Oral patholology, Oral radiology and Endododontics* **4**, 523-8

Qudeimat MA, Alyahya A, Hasan AA, Barrieshi-Nusair KM MTA (2016) Pulpotomy for permanent molars with clinical signs indicative of irreversible pulpitis: a preliminary study. *International Endodontic Journal* **4**, [Epub ahead of print]

Reeh ES, Messer HH, Douglas WH (1989) Reduction in tooth stiffness as a result of endodontic and restorative procedures. *Journal of Endodontics* **11**, 512-6.

Ricucci D, Loghin S, Siqueira J, Jr (2014) Correlation between Clinical and Histologic Pulp Diagnoses. *Journal of Endodontics* **40**, 1932–9.

Seltzer S, Bender IB (1963) The dynamics of pulp inflammation: correlations between diagnostic data and actual histologic findings in the pulp. *Oral Surgery, Oral Medicine, Oral Pathology* **16**, 846-71.

Simon S, Perard M, Zanini M, Smith AJ, Charpentier E, Djole SX, Lumley PJ (2013) Should pulp chamber pulpotomy be seen as a permanent treatment? Some preliminary thoughts. *International Endodontic Journal* **1**, 79-87.

Simon SR, Berdal A, Cooper PR, Lumley PJ, Tomson PL, Smith AJ (2011) Dentin-pulp complex regeneration: from lab to clinic. *Advances in Dental Research* **23**, 340-5.

Siqueira JF, Jr. (2001) Aetiology of root canal treatment failure: why well-treated teeth can fail. *International Endodontic Journal* **1**, 1-10.

Smith AJ, Duncan HF, Diogenes A, Simon S, Cooper PR (2016) Exploiting the Bioactive Properties of the Dentin-Pulp Complex in Regenerative Endodontics. *Journal of Endodontics* **1**, 47-56.

Smith AJ, Scheven BA, Takahashi Y, Ferracane JL, Shelton RM, Cooper PR (2012) Dentine as a bioactive extracellular matrix. *Archives of Oral Biology* **2**, 109-21.

Taha NA, B Ahmad M, Ghanim A (2015) Assessment of Mineral Trioxide Aggregate pulpotomy in mature permanent teeth with carious exposures. *International Endodontic Journal* Version of Record online: 30 JAN DOI: 10.1111/iej.12605

Tomson PL, Lumley PJ, Smith AJ, Cooper PR (2016) Growth factor release from dentine matrix by pulp capping agents promote pulp tissue repair-associated events. *International Endodontic Journal* Version of Record online: 14 MAR 2016.

van der Sluis L, Kidd E, Gruythuysen R, Peters L (2013) Preventive endodontics - an argument for avoiding root canal treatment. *ENDO - Endodontic Practice Today* **4**, 259-274.

Wu MK, Shemesh H, Wesselink PR (2009) Limitations of previously published systematic reviews evaluating the outcome of endodontic treatment. *International Endodontic Journal* **8**, 656-66.