Prevalence, predictive factors and clinical course of persistent pain associated with teeth displaying periapical healing following nonsurgical root canal treatment

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Prevalence, predictive factors, and clinical course of persistent pain associated with teeth displaying periapical healing following non-surgical root canal treatment: a prospective study.

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Running Title: Persistent pain or discomfort following non-surgical root canal treatment

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Abstract

Aims To investigate the prevalence, pain catastrophizing and other predictive factors, and clinical course of persistent pain/discomfort associated with teeth displaying periapical healing following non-surgical root canal treatment (NSRCT).

Methodology One-hundred-ninety-eight patients (264 teeth) who had NSRCT were reviewed at 5-14 months, post-operatively. Teeth with persistent pain or discomfort, plus evidence of periapical healing were further monitored 0.5, 4 & 10 years later. Pain Catastrophizing Scale (PCS) and Short Form of the McGill Pain Questionnaire (SF-MPQ) were completed. Predictive factors were investigated using logistic regression models.

Results Twenty-four per cent (60/249) of teeth displaying periapical healing at first review, were associated with persistent pain, or discomfort. Fifty-five teeth monitored 6-7 months later, were associated with a showed reduction in pain (17/30) or discomfort (7/25). CBCT of eight teeth with persistent symptoms and complete periapical healing (by conventional radiographs) revealed distinct, small apical radiolucencies (n = 3) or root-apex fenestration through the buccal plate (n = 2). History of chronic pain (headache, temporo-mandibular joint, masticatory muscle, neck, shoulder, or back pain) (*P* = 0.005), pre-operative pain (*P* = 0.04), responsive pulp (*P* = 0.009), tooth-crack (*P* = 0.05) and small periapical radiolucency (*P* = 0.005) were significant predictive factors. The PCS revealed 16 patients (22 teeth) ~~studied~~ were catastrophizers (PCS ≥30) but this had no influence on post-treatment symptoms (*P* = 0.5).

Conclusions Persistent pain or discomfort associated with teeth ~~showing~~ associated with periapical healing at the first review after NSRCT, decreased in intensity in most cases over the following 6-months. Longer-term follow-up ~~showed~~ revealed spontaneous improvement or symptom resolution in the majority of those with confirmed radiographic absence of periapical disease. Five predictive factors (history of chronic pain, teeth with responsive pulps, association with pain, diagnosis of tooth-crack before treatment, and diameter of pre-operative radiolucency) were identified.

Introduction

Persistent pain after root canal treatment (surgical or non-surgical) is often ~~taken~~ considered to be due to persistent periapical disease (Ng *et al.* 2008, ~~Ng *et al.*~~ 2011). However, ~~when~~ such symptoms ~~arise after root canal treatment~~ in the absence of overt clinical or radiographic evidence of persistent periapical or dental disease~~, it~~ may be indicative of other causes. Such manifestation is the subject of this study and has an average frequency ~~(pooled)~~ of 5-17 % of cases (Polycarpou *et al.* 2005, Klasser *et al.* 2011, Vena *et al.* 2014, Nixdorf *et al.* 2016).

Significant predictive factors influencing the persistence of pain after root canal treatment include: presence of pre-operative tooth pain, particularly that lasting more than 3 months; a history of systemic chronic pain problems; previous painful dental treatment; and female sex (Polycarpou *et al.* 2005, Nixdorf *et al.* 2010). ~~Conversely, patients' optimism about the treatment procedure may profoundly reduce the risk of persistent pain (Nixdorf *et al.* 2016).~~ In addition, individuals classified as catastrophizers, tend to magnify or exaggerate the threat-value or seriousness of the pain (Sullivan *et al.* 2005). It could be hypothesized that "pain catastrophizing" may contribute to their likelihood of reporting persistent pain. It is contended that patients may possibly be affected by this to the extent that they respond poorly to treatment, regardless of its immune-microbial effectiveness (Sullivan *et al.* 2005, Mankovsky *et al.* 2012). Conversely~~Conversely~~, patients' optimism about the treatment procedure may profoundly reduce the risk of persistent pain (Nixdorf *et al.* 2016). ~~It could be hypothesized that "pain catastrophizing" may contribute to their likelihood of reporting persistent pain. It is contended that patients may possibly be affected by this to the extent that they respond poorly to treatment, regardless of its immune-microbial effectiveness (Sullivan *et al.* 2005, Mankovsky *et al.* 2012).~~

The intensity of persistent pain after root canal treatment has been reported to vary from mild to moderate, with average intensities of 1.5±1.8 (based on 0-10 rating scale) ~~1.5±1.8 (Nixdorf *et al.* 2016)~~ over a 6-59 month post-treatment period (Nixdorf *et al.* 2016). Such low levels of persistent pain do not appear to have a large impact on those experiencing it (Nixdorf *et al.* 2016). Nevertheless, lack of insight about the cause of symptoms leads to anxiety that can be debilitating for some patients; a satisfactory and plausible explanation *alone* may suffice to resolve such anxieties and enable coping strategies (Pigg *et al.* 2013). Part of the key to resolving the diagnostic dilemma is to exclude the presence of persistent periapical disease with greater certainty. This requires the use of imaging techniques with better sensitivity, such as cone-beam computed tomography (CBCT) (Kanagasingam *et al.* 2017). The additional use of CBCT has been evaluated for its potential to differentiate "atypical odontalgia" from symptomatic apical periodontitis (Pigg *et al.* 2011). However, the periapical status of root [illegible] ~~canal treated~~ teeth with chronic persistent pain has not been explored by CBCT in previous studies (Polycarpou *et al.* 2005, Klasser *et al.* 2011, Vena *et al.* 2014, Nixdorf *et al.* 2016); nor has the long-term clinical course of such persistent pain/discomfort been systematically analysed, to better inform decision-making on management options.

The three-fold aims of this study were to investigate the: (1) prevalence; (2) pain catastrophizing and other predictive factors; and (3) clinical course, of persistent pain or discomfort associated with teeth exhibiting evidence of periapical healing following non-surgical root canal treatment.

Materials and methods

Ethical approval, inclusion & exclusion criteria

This study was approved by the Joint Research & Ethics Committee of UCL Hospitals NHS Trust (Reference number 96/E195). Informed consent was obtained from all patients.

Patients who had primary (*de novo / first time*) or secondary (*retreatment*) non-surgical root canal treatment of a permanent tooth completed ~~by staff or postgraduate students~~ in the Department of Endodontology, Eastman Dental Hospital, ~~)~~University College London Hospital, London, UK, between 1st July 2006 and 30th November 2007, were included.

All patients fulfilling the ~~above~~ inclusion criteria were invited to attend the first follow-up appointment between 6 and 12 months following completion of root canal treatment. Patients who failed to attend the first review appointment, those who were less than sixteen years old by the first review appointment, or were unable to complete the relevant questionnaires, were excluded. Teeth associated with pre-operative advanced periodontal bone loss to the apical third were also excluded.

Teeth exhibiting symptoms (pain or discomfort), coupled with radiographic evidence of periapical healing at the first review appointment, were reviewed 6-7 months later. Those failing to attend were excluded from the second part of the analyses. Patients presenting with root filled ~~root-treated~~ teeth with persistent ~~pain or discomfort~~symptoms, as well as complete periapical healing were further monitored at 4 and 10 years after treatment.

Sample size estimation

A minimum sample size of 200 patients/teeth with clinical and radiographic evidence of periapical healing (complete or incomplete reduction of periapical radiolucency at first review) was established based on a similar study (Polycarpou *et al.* 2005).

Polycarpou *et al.* (2005) included 103 patients ~~judged to have successfully~~ with root-filled ~~treated~~ teeth exhibiting ~~based on~~ periapical healing, as well as persistent pain ~~status, of which~~ in 20% ~~had persistent pain~~. The sample size of 200 was deemed to ~~should~~ provide sufficient power for inclusion of 4 explanatory variables in the same logistic regression model, assuming 20% of ~~positive~~ cases exhibited ~~(presence of pain/discomfort~~symptoms (Peduzzi *et al.* 1996).~~)~~

Follow-up clinical and radiographic examination

Follow-up assessments of patients were performed by two authors (RP & Y-LN), consisting of updating medical history, routine history-taking, and clinical plus periapical radiographic examination of the studied teeth. Extra-oral examination included clinical examination of the face, head and neck (~~for~~ asymmetry, ~~and~~ tender points, ~~along with~~ auscultation and palpation of the temporomandibular joints and ~~an~~ assessment of ~~the range of~~ mandibular movement~~tions~~s). Intra-oral examination included an assessment of the patients' occlusion and any interferences on the root-filled ~~treated~~ teeth. Clinical details recorded included: tenderness ~~to palpation~~ of the adjacent soft tissues, presence/absence of a swelling, sinus tract, periodontal probing depths, tenderness to pressure or percussion of the tooth, and integrity of the restoration margin. Any signs or symptoms originating from adjacent teeth were assessed and accounted for.

Following the assessment, the ~~clinician interviewed the~~ patient was interviewed to complete a modified version of the Short Form of the McGill Pain Questionnaire (SF-MPQ), and the Pain Catastrophizing Scale. Four additional pain descriptor terms were added to the SF-MPQ: *tingling*, *numbness*, *sensitivity*, and *itching*.

Periapical radiographs were taken, ~~attempting to~~ reproducing as closely as possible, ~~e~~ the angulation of the immediate post-operative radiographs. Rinn paralleling devices (Dentsply Limited, Weybridge, ~~Surrey~~, UK) and Kodak F-speed double radiographic films (Eastman Kodak Company, Rochester, NY, USA) were used and manually processed.

In addition, as part of the routine clinical care, those teeth associated with persistent symptoms ~~pain/discomfort~~ at the second review but showing evidence of complete radiographic healing were consented and subjected to cone-beam computed tomography (CBCT) scans to rule out post-treatment periapical disease as the origin of symptoms. CBCT exposures were undertaken using the Veraview Epocs 3D scanner (J. Morita M manufacturing C corporation, Kyoto, Japan). All doses were as low as reasonably practical in compliance with Ionising Radiation (Medical exposure) Regulations (IRMER 2000). The field of view was limited (4 × 4 cm) and encompassed the target and adjacent teeth and their surrounding structures. The optimum exposure time (High-resolution mode, 15.8s), tube current (3.5 to 4.5 mA), energy/potential (90.0 Kv), and reconstruction resolution (voxel size 0.08 mm) were used to acquire an image of adequate diagnostic quality. The zoom reconstruction feature was also used on critical areas; CBCT data were re-sliced using 0.08 mm slice intervals and 1.5 mm slice thickness.

Viewing of periapical radiographs and CBCT

The two observers (RP & YLN) were pre-calibrated using a selection of 12 radiographs, three in each radiographic healing category (~~Table 1~~Complete healing, incomplete healing, failure, or uncertain). One observer (RP) then examined all the radiographs on two separate occasions on a standard Rinn fluorescent lightbox (Dentsply Ltd), under 2.5× magnification using a Brynolf viewer (Brynolf, Trycare limited, Bradford, UK), in a darkened room. One third (33%) of the radiographs were independently examined by the second observer (YLN) under the same conditions to determine inter-observer agreement on periapical healing outcome. Disagreements on decisions were resolved to agreement through discussion. One observer (RP) independently recorded the pre-operative size of the periapical radiolucency, along with the apical extent of the root-filling in relation to the radiographic apex, and presence of any extruded sealer. In multi-rooted teeth, the root with the worst outcome (highest score) of each parameter was recorded for the tooth: periapical status (intact periodontal ligament space=0, reduction in lesion size but PDL not intact=1, lesion size remained the same or increased=2), apical extent of root filling (0-2 mm within the radiographic apex=0, > 2mm short of radiographic apex=1, extruded beyond the radiographic apex=2), and presence of sealer extrusion (absent = 0, presence=1). All CBCT images were reported on by a Consultant radiologist blinded to the study, and included any pathosis associated with the target and adjacent teeth, and their associated anatomical structures.

? area / volume !

Data management and analysis

Statistical analyses were performed using a computer statistics package (SPSS 15.0 for Windows; SPSS Inc. Chicago, IL, USA, 2006). The Cohen's kappa coefficient was calculated to assess both inter- and intra-observer reliability in determination of radiographic healing outcome. Good agreement was taken as >0.8, substantial as 0.61-0.8, and moderate 0.4-0.6 (Petrie & Watson 1999).

The internal consistency of the SF-MPQ was evaluated using the Chronbach's α and was considered acceptable if α was 0.7 or higher (Tavakol & Dennick 2011).

Pain intensities were calculated based on four measures from the SF-MPQ: (1) Visual Analogue Scale score from 0-10 rating scale; (2) Sum of scores from evaluative (0-5) and VAS scales (0-10) of SF-MPQ; (3) Total score from the descriptor section of the SF-MPQ (score of 0-3 for each of the 19 descriptors); and

(4) Number of Words Chosen (NWC) (maximum 19). It was noted that two distinct types of symptoms ~~(pain *versus* discomfort)~~ were reported, pain or discomfort. The proportion of teeth associated with pain (SF-MPQ pain VAS score > 0) or discomfort (SF-MPQ pain VAS score = 0, plus individual descriptor score > 0) was therefore calculated for each periapical healing category. Changes in pain or discomfort experience were calculated based on changes in VAS scores, or total SF-MPQ scores between appointments, respectively~~ while changes in discomfort were calculated based on total SF-MPQ scores in patients who had scored zero on the VAS~~.

~~Total scores on the Pain Catastrophizing Scale (PCS) for each patient; and the median scores for all the teeth and for a subset of teeth associated with complete or incomplete healing were calculated.~~

Bivariate associations of putative predictors with “symptoms” (pain or discomfort data pooled) at the first review appointment~~,~~ was assessed~~used for screening independent variables for possible inclusion in_ multi-variable logistic regression modelling~~. Those~~Independent~~ variables showing significant association with “symptoms” at the 10% ~~significance~~ level were included in the multi-variable regression modelling. The odds ratios (ORs) and 95% confidence intervals (CIs) for assessing the strength of association~~ between potential predictors and the outcome of interest, “symptoms”~~, were estimated using the robust estimator for standard errors (Desai *et al.* 2013) to account for the clustering effect of multiple teeth nested within the same patient.

Results

Of the inception cohort of 288 patients fulfilling the inclusion criteria, 198 patients (264 teeth) attended the first (5-14 month post-operative) review, representing a recall rate of 69%.

The intra-observer reliability in determining~~ation of~~ the periapical status at ~~the~~ first review was substantial (kappa coefficient = 0.8; 95% CI: 0.7, 0.8). The inter-observer agreement based on 33% of the teeth improved from the first (kappa coefficient = 0.6; 95% CI: 0.4, 0.7) to the second (kappa coefficient = 0.97; 95% CI: 0.9, 1.0) reading.

The SF-MPQ demonstrated high internal consistency for the ~~present~~ cohort (Cronbach's α = 0.880). The alpha-if-item-deleted statistics showed that removing individual descriptors led to a reduction in Cronbach's α, with the exception of the descriptor "itching" (the removal of which did not change the α value).

Frequency and clinical course of post-treatment symptoms

At the first review, 25% of teeth displaying complete or incomplete periapical healing (62/249) were associated with either pain (n=34; SF-MPQ pain VAS score > 0) or discomfort (n=28; SF-MPQ pain VAS score = 0, plus individual descriptor score > 0) (Table ~~2~~1). The average "pain" intensity reported for the 34 teeth is presented in Table ~~3~~2. The frequency distribution of descriptor choice at the first review is presented in Appendix I.

The second review assessed 55 teeth in 48 patients who had shown~~ed~~ signs of periapical healing with~~plus~~ persistent symptoms~~pain or discomfort~~ at the first review. The clinical course of the pain or discomfort is detailed in figures 1 and 2. Of the 30 teeth reviewed further~~ (Figure 1)~~, the pain intensity had decreased or disappeared for the majority (n= 23, 77%) (Figure 1 – see *footnote). Of the 25 teeth associated with signs of periapical healing plus discomfort reviewed further~~ (Figure 2)~~, the discomfort had decreased in intensity or disappeared in 80% (n=20), but had become worse or painful in 12% (n=3) (Figure 2 – see *footnote). All ~~the teeth without~~ pain-free teeth ~~but~~ displaying healing ~~healing~~ at the first review and had further follow-ups (1-4 year) (complete = ~~(~~45/49 teeth; ~~) or~~ incomplete = ~~(~~105/138), remained symptom-free ~~at further 1-4 year follow-ups (1-4 year)~~(Table 1).

Of the 10 periapically "healed" teeth (in 10 patients) ~~judged to be periapically "healed" but associated~~ with persistent symptoms (pain/discomfort) at the second review, eight were subjected to CBCT scans ~~in 2007/8~~. The CBCT scans revealed no ~~obvious~~ apical pathosis associated with 3 teeth (38%), small ~~but distinct~~ apical radiolucencies associated with 2 teeth (25%), and root apices "fenestrating" the buccal cortical plate in ~~of~~ 3 teeth (37.5%) ~~"fenestrating" the buccal cortical plate, rendering radiographic diagnosis of the apical status impossible~~.

The characteristics of these patients are presented in appendix II. Nine ~~out~~ of the ten patients ~~were~~ contacted 10 years later ~~in 2017~~, ~~seven~~ reported freedom from any symptoms (n=7), ~~one reported~~ a different sensation (n=1), and ~~one reported~~ persistent "discomfort" (n=1)~~associated with the root-treated tooth~~.

Influence of "catastrophizing" on post-treatment symptoms

The PCS scores (mean = 11.8; 95% CI: 10.3, 13.3) revealed ~~that~~ only 16 patients (22 teeth) to be ~~were classified as~~ catastrophizers (PCS ≥ 30). Bivariate analysis showed~~revealed~~ catastrophizing ~~did~~ not to have significant (*P* = 0.5) predictive value for post-treatment symptoms ~~at the first review.~~. The factor was therefore not analysed further.

Predictive factors for coincidence of periapical~~ly healed/~~healing ~~teeth with~~ and symptoms at ~~the~~ first review

Single variable logistic regression models including data from teeth with~~displaying~~ ~~some degree of~~ periapical healing (n = 249) at ~~the~~ first review, revealed eight potential predictive factors (Appendix III). Several potential predictive factors ~~showed~~ had a significant correlation between them and could not be entered into the same model simultaneously due to collinearity~~Appendix III~~.

The final two multivariable logistic regression models (Table 3) revealed the odds for ~~teeth in~~ patients with a history of chronic pain ~~problems~~ (head, temporo-mandibular ~~joint/muscle~~, neck, shoulder, or back pain) to be associated with persistent tooth symptoms was 3.5-fold higher than for ~~teeth in~~ patients without ~~no~~ such history (OR = 3.5; 95% CI: 1.5, 8.4). Teeth with ~~pulps~~ responsive pulps ~~to pulp tests~~ before treatment ~~were~~ had 5-fold higher odds of ~~more likely to be associated with~~ persistent symptoms (OR = 5.2; 95% CI: 1.5, 18.1). Teeth ~~associated~~ with pre-operative pain had 2.9 times higher ~~risk~~ odds of persistent symptoms (OR = 2.9; 95% CI: 1.1, 8.1). With each millimetre increase in diameter of pre-operative radiolucency, the ~~risk~~ odds of persistent symptoms were~~as~~ reduced by 13% (OR = 0.87; 95% CI: 0.78, 0.97). Presence of crack only retained its predictive value at the 10 % level.

Discussion

The ~~final~~ sample size (198 patients/264 teeth) and recall rate (69 %) ~~of the present study~~ were comparable to ~~similar~~ previous studies, in which ~~where~~ samples ~~sizes~~ ranged from 7 to 276 teeth (Vickers *et al.* 1998, Polycarpou *et al.* 2005, Nixdorf *et al.* 2010, Klasser *et al.* 2011). A ~~study on~~ persistent pain study ~~conducted~~ in general practice~~s within a research network~~ (Nixdorf *et al.* 2016) had~~included~~ a substantially larger cohort (651 cases) but their pre-operative diagnosis~~tic data~~ and post-treatment periapical healing status were not presented~~ or analysed~~.

~~Inclusion of patients with~~ Contribution of more than one ~~treated~~ tooth per patient ~~may~~ complicates and confounds the analyses without special statistical measures. The present study accounted for any~~the~~ clustering effect of multiple teeth within the same patient in the regression models. This approach allowed investigation of ~~the effect of~~ several associated factors including whether: multiple teeth received root canal treatment (OR = 1.3; 95% CI: 0.7, 2.6), multiple treated teeth were adjacent to each other (OR = 1.1; 95% CI: 0.5, 2.6), or in the same (OR = 0.8; 95% CI: 0.3, 2.2), or opposing (OR = 0.7; 95% CI: 0.2, 2.0) arches. Previous studies had resolved the problem by randomly selecting ~~only~~ one tooth per patient for analyses (Polycarpou *et al.* 2005, Vena *et al.* 2014, Nixdorf *et al.* 2015) but~~. T~~ this ~~approach may~~ risks losing~~e~~ valuable information.~~ in the process.~~ ~~The present study accounted for the clustering effect of multiple teeth within the same patient in the regression models. This approach allowed investigation of the effect of several associated factors including whether: multiple teeth received root canal treatment (OR = 1.3; 95% CI: 0.7, 2.6), multiple treated teeth were adjacent to each other (OR = 1.1; 95% CI: 0.5, 2.6), or in the same (OR = 0.8; 95% CI: 0.3, 2.2), or opposing (OR = 0.7; 95% CI: 0.2, 2.0) arches.~~

The Short Form McGill Pain Questionnaire (SF-MPQ) was adopted with the addition of four ~~additional~~ terms: tingling, numbness, sensitivity and itching because ~~it was surmised that~~ these terms may ~~help~~ describe ~~sensations~~ common sensations during wound healing (Marbach 1978, Bates & Stewart 1991, Henderson *et al.* 2006). Addition of all except "itching" could be justified based on alpha-if-item-deleted statistics. ~~-~~Symptoms of~~such as~~ anaesthesia, pruritis or pain, associated with ~~mature~~ scarring~~s,~~ have been attributed to increased densities of mediators, SP and CGRP in healing wounds (Henderson *et al.* 2006). The descriptor, "~~I~~itching" was ~~only~~ selected by only two patients but ~~the term~~ has been used ~~by patients~~ to describe pain ~~ultimately~~ diagnosed as “atypical odontalgia” (Marbach 1978, Bates & Stewart 1991). Twenty-nine patients specifically distinguished the experience of *discomfort* from *pain* associated with a root-~~treated~~filled tooth. This distinction, in the authors’ experience, is often volunteered by patients and sometimes authoritatively corrected when an alternative~~the other~~ term is used synonymously. The fact that patients independently make the~~This~~ distinction~~, made~~ with such clarity and authority points to a potential biological difference that may have ~~by patients seems to have~~ been overlooked in the literature. Consequently, there is no validated questionnaire to measure “discomfort”. The SF-MPQ incidentally did classify patients into those experiencing pain or discomfort and sought not to mix the two groups. Consistently, all patients experiencing *discomfort* scored zero on the VAS, but scored positively for selected descriptors on the SF-MPQ. The SF-MPQ may therefore be a suitable instrument for measuring discomfort but further formal validation is warranted. Nevertheless~~However~~, the pain or discomfort data were pooled under “symptom” for ~~analysis of predictive factors~~ binary logistical regression due to~~as there was~~ insufficient statistical power for multinomial regression to investigate whether the two types of symptoms had different sets of predictive factors.

The frequency of persistent tooth pain~~teeth associated with pain~~ (14%) amongst the study cohort was more-or-less consistent with ~~the findings by~~ Nixdorf *et al.* (2016), who~~. They~~ found that ~~that~~ 10% of ~~their~~ patients reported pain ~~at~~ 6 months post-operatively, regardless of periapical status. In the present study, the majority of teeth diagnosed with post-treatment periapical disease were asymptomatic (82%), in agreement with Polycarpou *et al.* (2005). Nixdorf *et al.* (2015) reported that ~~in their cohort,~~when persistent tooth pain ~~in 37% of the patients~~ was attributed to symptomatic apical periodontitis (37%),~~but~~ the source emanated from an adjacent tooth in ~~half of~~ their cases. Such an association was not found in the present cohort~~, any symptoms originated from the adjacent teeth were excluded in the analyses~~. ~~The p~~Persistent~~ce of~~ symptoms long after technically adequate~~successful~~ root canal treatment may ~~also~~ be attributed to non-odontogenic problems (Nixdorf *et al.* 2015), such as ~~-~~Persistent Dentoalveolar Pain Disorder (PDAP)~~ with no objective signs of pathosis, also termed~~ (or atypical facial neuralgia, ~~or~~ atypical odontalgia) (Marbach *et al.* 1982); trigeminal neuralgia (Law & Lilly 1995); temporomandibular disorder (Nixdorf *et al.* 2015), or~~and~~ headache (Alonso & Nixdorf 2006)~~ are the most commonly reported~~.

~~PDAP is a neuropathic pain condition due to underlying dysfunction of the somatosensory system as a result of nerve damage (Baad-Hansen et al. 2013).~~ All 16 symptomatic cases with~~that demonstrated~~ complete periapical healing at ~~the~~ first review in the present study fulfilled the PDAP diagnostic criteria (Nixdorf *et al.* 2012). ~~All t~~These patients had ~~experienced~~ continuous or recurrent pre-operative and persistent post-treatment symptoms lasting ~~for~~ more than 6 months, ~~and~~ located around the root-filled~~treated~~ tooth without clinical and radiographic signs of pathosis. They also presented with other chronic pain problems~~ including headache, TMD, neck, shoulder, or back pain~~.

Spontaneous improvement or resolution of PDAP, as apparently found in the present study, has not previously been reported. Therefore, either the teeth in the present cohort should not be diagnosed with PDAP (but given~~with~~ another label), or the criteria for PDAP should be modified to include~~account for~~ the possibility of subsequent spontaneous resolution. Pigg *et al.* (2013) reported that one-third of patients diagnosed with "atypical odontalgia" perceived considerable improvement, and 10% became pain-free over a seven-year time-frame, after ~~receiving~~ various ~~types of~~ interventions. ~~In the present study, despite the negative CBCT and clinical findings on teeth associated with symptoms, it may be speculated that periapical healing may actually have been incomplete at a microscopic/molecular level in a proportion of cases. This may account for spontaneous improvement in symptoms in these cases as healing then truly progressed to completion. Pain experience related to transition from the inflammatory to the proliferative phase of wound healing could be attributed to mediation through sensory neuropeptides~~ It is not implausible that contemporary diagnostic aids fail to detect tissue and molecular level inflammation, the undetected resolution of which may then abolish symptoms. ~~(Brain 1997, Gunjigake *et al.* 2006) or sensory re-innervation of scars (Henderson *et al.* 2006). The s~~ Spontaneous improvement may~~could~~ also be related to ~~attributed to~~ patients' tolerance~~acceptance~~ of the symptoms through a satisfying ~~chronic pain after receiving satisfactory~~ explanation (Pigg *et al.* 2013), or ~~and~~ development of coping strategies (Wolf *et al.* 2006). ~~or attributable to their low intensity of their symptoms (Pigg *et al.* 2013). Pigg *et al.* (2013) reported that half of the patients diagnosed with "atypical odontalgia" were dissatisfied with their pain explanation at consultation. A larger proportion was, however, satisfied with the explanation amongst those showing symptom improvement compared to those not. The present study did not measure patients' satisfaction with their pain explanation but all those interviewed by phone 10 years later (in 2017) expressed satisfaction and contentment with the overall care received. Pigg *et al.* (2013) reported that low baseline pain intensity was a predictor of a favourable pain intervention outcome. The spontaneous improvement evident in this study may possibly reflect this phenomenon since a proportion had relatively low intensity symptoms.~~

~~The present study identified f~~Five significant ~~predictive~~ factors predicted~~for the occurrence of~~ symptoms associated with ~~amongst~~ root-~~treated~~ filled teeth displaying periapical healing~~ at review. They were~~: (1) history of systemic chronic pain; (2) pre-operative tooth pain; (3) ~~presence of~~ pre-operative tooth-crack; (4) teeth with ~~pulps~~ responsive pulps~~to pulp tests~~; and (5) pre-operative size of periapical radiolucency. Two ~~of the~~ predictors (~~:~~ history of chronic pain~~ disorder~~ [$P = 0.005$]~~,~~ and pre-treatment tooth pain [$P = 0.04$])~~;~~ were ~~also~~ previously reported by Polycarpou *et al.* (2005). The present study~~, however,~~ did not investigate the influence of ~~duration of~~ pre-treatment pain duration, ~~which was found to be~~ a significant predictor in other studies (Perkins & Kehlet 2000, Mattscheck *et al.* 2001, Nixdorf *et al.* 2016). ~~The~~ H~~h~~istory of chronic non-odontogenic pain and ~~the presence of~~ pre-operative pain ~~were found to~~ had~~ve~~ significant correlation with each other ($P < 0.0001$), ~~. It may be hypothesized that these two factors were in~~possibly suggesting a chain confounding relationship~~pathway; that patients suffering from chronic pain were more likely to experience pre-treatment tooth pain~~. Alternatively, pain development ~~of pain~~ may have ~~be~~ genetic susceptibility~~ally governed~~ (Dominguez *et al.* 2008, Binkley *et al.* 2009, Dominguez *et al.* 2012).

~~found to be limited to the level above the canal orifice, without any associated periodontal probing defects. Persistent pain in the cases with cracks detected pre-operatively, coupled with complete periapical healing at the first review, might have been of periodontal original as a result of tooth flexure under occlusal stress. This is supported by the observation that the symptoms resolved at the second review, by which stage they had been restored with full veneer cast restorations.~~ Teeth with ~~pulps~~ responsive pulps ~~*to pulp tests*~~ diagnosed with irreversible pulpitis may trigger nociceptive signals~~nerve fibres~~ at the root apex but ~~such pain~~ should ~~theoretically~~

resolve after root canal treatment unless ~~. Such triggering, can however, initiate a~~a deafferentation response was initiated~~in which the apical nerves become hypersensitive resulting in “atypical odontalgia”~~ (Marbach 1996). ~~That Tthe *size of the* periapical lesion~~ size ~~was found to be a~~a ~~negative predictive factor. This finding is consistent with a previous study investigating prevalence of post-operative pain 2 days after root canal treatment (Ng *et al.* 2004), and~~ explained by ~~attributed to accommodation of any increased~~ inflammatory ~~pressure due to inflammatory exudate by the space afforded by incomplete periapical healing.~~

In ~~summary,~~ this study, ~~showed that a considerable percentage (~~25%~~)~~ of patients ~~was still~~ experienc~~ing~~ed some form of post-operative sensation ~~(perceived as either pain or discomfort) five to fourteen~~5-14 months after~~following~~ root canal treatment. ~~This would undoubtedly pose uncertainty in the mind of both the dentist and patient about the treatment efficacy. Furthermore, it is likely to lead to delay in the placement of a cast restoration on a tooth with seemingly unexplained pain.~~ Knowledge of the true prevalence of ~~symptoms~~ prolonged symptoms after ~~(pain or discomfort) following~~ root canal treatment would aid ~~and thus~~ appropriate management ~~counselling at the time of treatment planning may help to smoothen the post-operative management~~ of patient~~'s~~ expectations, particularly in the presence of identifiable predictive factors ~~and anxieties~~. ~~Equally, in the absence of such prior counselling, the ability to advise that persistent pain in a small proportion of patients is normal and would resolve spontaneously over time, is a valuable tool, in particular for those patients displaying the identified predictive factors. A clear explanation of the reasons for such sensations is crucial in enabling patients to cope with the discomfort and to avoid unnecessary intervention.~~

Conclusion

Persistent pain or discomfort associated with teeth showing periapical healing at first review after non-surgical root canal treatment decreased in intensity in most cases over the following 6-months. Longer-term follow-up ~~showed~~ revealed spontaneous improvement or resolution of symptoms in the majority of those with confirmed absence of periapical disease. Five predictive factors (history of chronic pain ~~problems~~, teeth responsive to pulp tests, teeth associated with pre-operative pain, ~~presence of~~ tooth-crack prior to treatment, and diameter of pre-operative radiolucency) were identified.

Figure legends

Figure 1. Flow chart outlining the clinical course of pain from teeth associated with evidence of healing from the first to the second review appointment.

Figure 2. Flow chart outlining the clinical course of discomfort from teeth associated with evidence of healing from the first to the second review appointment.

Table legends

~~Table 1. Criteria for periapical healing.~~

Table ~~2~~1. Frequency distribution of pain or discomfort presenting at the first (n=264 teeth) and second (n=55 teeth) review appointments, stratified by various periapical healing outcomes.

Table ~~3~~2. Intensity of pain (based on the SF-MPQ records) associated with teeth with periapical healing ("complete" or "incomplete") at the first review.

Table 3. Multi-variable logistic regression models incorporating presence of pain/discomfort as the binary dependent variable, and "history of chronic pain" (Model 1), or "pre-operative pain" (Model 2), and simultaneously with another three significant explanatory variables.

~~**Appendix legends**~~ Supplementary material - online only

Table S1 ~~**Appendix I**~~**.** Frequency distribution of choice of descriptors on the SF-MPQ at first review (n=260).

Table S2 ~~**Appendix II**~~**.** Characteristics of patients experiencing persistent pain/discomfort associated with their root-treated tooth at the second review (11-20 months post-operatively), and their experience at 4 years (2011), and 10 years (2017) later.

Table S3 ~~**Appendix III**~~**.** Single logistic regression models investigating the association between potential predictive factors and symptoms experienced at the first review (n = 249 teeth displaying evidence of periapical healing)