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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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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 post-treatment 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, ~~showed~~ were associated with 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 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, such symptoms in the absence of overt clinical or radiographic evidence of persistent periapical or dental disease may be indicative of other causes. Such manifestation is the subject of this study and has an average frequency 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). 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, patients' optimism about the treatment procedure may profoundly reduce the risk of persistent pain (Nixdorf *et al.* 2016).

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) 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~~ root ~~canal treated~~filled 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 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 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-treated~~root-filled teeth with persistent 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 with root-~~treated~~ filled teeth exhibiting periapical healing, as well as persistent pain in 20%. The sample size of 200 was deemed ~~to provide~~ sufficient ~~power for~~ to obtain a reliable prediction model with ~~inclusion of~~ 4 explanatory variables ~~in the same logistic regression model~~, assuming 20% of cases exhibited 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 (asymmetry, tender points, auscultation and palpation of the temporomandibular joints and assessment of mandibular movements). Intra-oral examination included an assessment of the patients' occlusion and any interferences on the root-~~treated~~ filled teeth. Clinical details recorded included: tenderness 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 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, reproducing as closely as possible, 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 manually.

In addition, as part of the routine clinical care, those teeth associated with persistent symptoms 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 (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~~ diameter 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.

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 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.

Bivariate associations of putative predictors with "symptoms" (pain or discomfort data pooled) at the first review appointment was assessed. Those variables showing significant association with "symptoms" at the 10% level were included in the multi-variable regression modelling. The odds ratios (ORs) and 95% confidence intervals (CIs) for assessing the strength of association, 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 the periapical status at 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 cohort (Cronbach's $\alpha = 0.880$). 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 1). The average "pain" intensity reported for the 34 teeth is presented in Table 2. The frequency distribution of descriptor choice at the first review is presented in ~~Appendix~~ Table ~~I~~S1.

The second review assessed 55 teeth in 48 patients who had shown signs of periapical healing with persistent symptoms at the first review. The clinical course of the pain or discomfort is detailed in ~~f~~Figures 1 and 2. Of the 30 teeth reviewed further, 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, 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 pain-free teeth displaying healing at the first review and had further follow-ups (1-4 year) (complete = 45/49 teeth; incomplete = 105/138), remained symptom-free (Table 1).

Of the 10 periapically "healed" teeth (in 10 patients) with persistent symptoms (pain/discomfort) at the second review, eight were subjected to CBCT scans. The CBCT scans revealed no apical pathosis associated with 3 teeth (38%), small apical radiolucencies associated with 2 teeth (25%), and root apices "fenestrating" the buccal cortical plate in 3 teeth (37.5%).

The characteristics of these patients are presented in ~~appendix II~~Table S2. Nine of the ten patients contacted 10 years later, reported freedom from any symptoms (n=7), a different sensation (n=1), and persistent "discomfort" (n=1).

Influence of "catastrophizing" on post-treatment symptoms

The PCS scores (mean = 11.8; 95% CI: 10.3, 13.3) revealed only 16 patients (22 teeth) to be catastrophizers (PCS ≥ 30). Bivariate analysis showed catastrophizing not to have significant (*P* =

0.5) predictive value for post-treatment symptoms. The factor was therefore not analysed further.

Predictive factors for coincidence of periapical healing and symptoms at first review

Single variable logistic regression models including data from teeth with periapical healing (n = 249) at first review, revealed eight potential predictive factors (~~Appendix III~~Table S3). Several potential predictive factors ~~showed~~ had a significant correlation between them and could not be entered into the same model simultaneously due to collinearity.

The final two multivariable logistic regression models (Table 3) revealed the odds for patients with a history of chronic pain (head, temporo-mandibular, neck, shoulder, or back pain) to be associated with persistent tooth symptoms was 3.5-fold higher than for patients without such history (OR = 3.5; 95% CI: 1.5, 8.4). Teeth with responsive pulps before treatment had 5-fold higher odds of persistent symptoms (OR = 5.2; 95% CI: 1.5, 18.1). Teeth with pre-operative pain had 2.9 times higher odds of persistent symptoms (OR = 2.9; 95% CI: 1.1, 8.1). With each millimetre increase in diameter of pre-operative radiolucency, the odds of persistent symptoms were 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 sample size (198 patients/264 teeth) and recall rate (69 %) were comparable to previous studies, in which samples ranged from 7 to 276 teeth (Vickers *et al.* 1998, Polycarpou *et al.* 2005, Nixdorf *et al.* 2010, Klasser *et al.* 2011). A persistent pain study in general practice (Nixdorf *et al.* 2016) had a substantially larger cohort (651 cases) but their pre-operative diagnosis and post-treatment periapical healing status were not presented.

Contribution of more than one tooth per patient complicates and confounds the analyses without special statistical measures. The present study accounted for any clustering effect of multiple teeth within the same patient in the regression models. This approach allowed investigation 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 one tooth per patient for analyses (Polycarpou *et al.* 2005, Vena *et al.* 2014, Nixdorf *et al.* 2015) but this risks losing valuable information.

The Short Form McGill Pain Questionnaire (SF-MPQ) was adopted with the addition of four terms: tingling, numbness, sensitivity and itching because these terms may describe 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 anaesthesia, pruritis or pain, associated with scarring have been attributed to increased densities of mediators, SP and CGRP in healing wounds (Henderson *et al*. 2006). The descriptor, "itching" was selected by only two patients but has been used to describe pain 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 term is used synonymously. The fact that patients independently make the distinction with such clarity and authority points to a potential biological difference that may 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, the pain or discomfort data were pooled under "symptom" for binary logistical regression due to 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 (14%) amongst the study cohort was more-or-less consistent with Nixdorf *et al*. (2016), who found that 10% of patients reported pain 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 when persistent tooth pain was attributed to symptomatic apical periodontitis (37%), the source emanated from an adjacent tooth in their cases. Such an association was not found in the present cohort.

Persistent symptoms long after technically adequate root canal treatment may be attributed to non-odontogenic problems (Nixdorf *et al.* 2015), such as Persistent Dentoalveolar Pain Disorder (PDAP) (or atypical facial neuralgia, atypical odontalgia) (Marbach *et al.* 1982); trigeminal neuralgia (Law & Lilly 1995); temporomandibular disorder (Nixdorf *et al.* 2015), or headache (Alonso & Nixdorf 2006).

All 16 symptomatic cases with complete periapical healing at first review in the present study fulfilled the PDAP diagnostic criteria (Nixdorf *et al.* 2012). These patients had continuous or

recurrent pre-operative and persistent post-treatment symptoms lasting more than 6 months, located around the root-~~treated~~ filled tooth without clinical and radiographic signs of pathosis. They also presented with other chronic pain problems.

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 another label), or the criteria for PDAP should be modified to include 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 various interventions. 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. Spontaneous improvement may also be related to patients' tolerance of the symptoms through a satisfying explanation (Pigg *et al.* 2013), or development of coping strategies (Wolf *et al.* 2006).

Five significant factors predicted symptoms associated with root-~~treated~~ filled teeth displaying periapical healing: (1) history of systemic chronic pain; (2) pre-operative tooth pain; (3) pre-operative tooth-crack; (4) teeth with responsive pulps; and (5) pre-operative size of periapical radiolucency. Two predictors (history of chronic pain [$P = 0.005$] and pre-treatment tooth pain [$P = 0.04$]) were previously reported by Polycarpou *et al.* (2005). The present study did not investigate the influence of pre-treatment pain duration, a significant predictor in other studies (Perkins & Kehlet 2000, Mattscheck *et al.* 2001, Nixdorf *et al.* 2016). History of chronic non-odontogenic pain and pre-operative pain had significant correlation with each other ($P < 0.0001$),

possibly suggesting a chain confounding relationship. Alternatively, pain development may have genetic susceptibility (Dominguez *et al.* 2008, Binkley *et al.* 2009, Dominguez *et al.* 2012).

Teeth with responsive pulps diagnosed with irreversible pulpitis may trigger nociceptive signals at the root apex but should resolve after root canal treatment unless a deafferentation response was initiated (Marbach 1996).

In this study, 25% of patients experienced some form of post-operative sensation 5-14 months after root canal treatment. Knowledge of the true prevalence of prolonged symptoms after root canal treatment would aid appropriate management of patient expectations, particularly in the presence of identifiable predictive factors.

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, teeth responsive to pulp tests, teeth associated with pre-operative pain, 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.** 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 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

~~Appendix~~ Table S~~I~~1. Frequency distribution of choice of descriptors on the SF-MPQ at first review (n=260).

~~Appendix II~~Table S2. 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.

~~Appendix III~~Table S3. 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)

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

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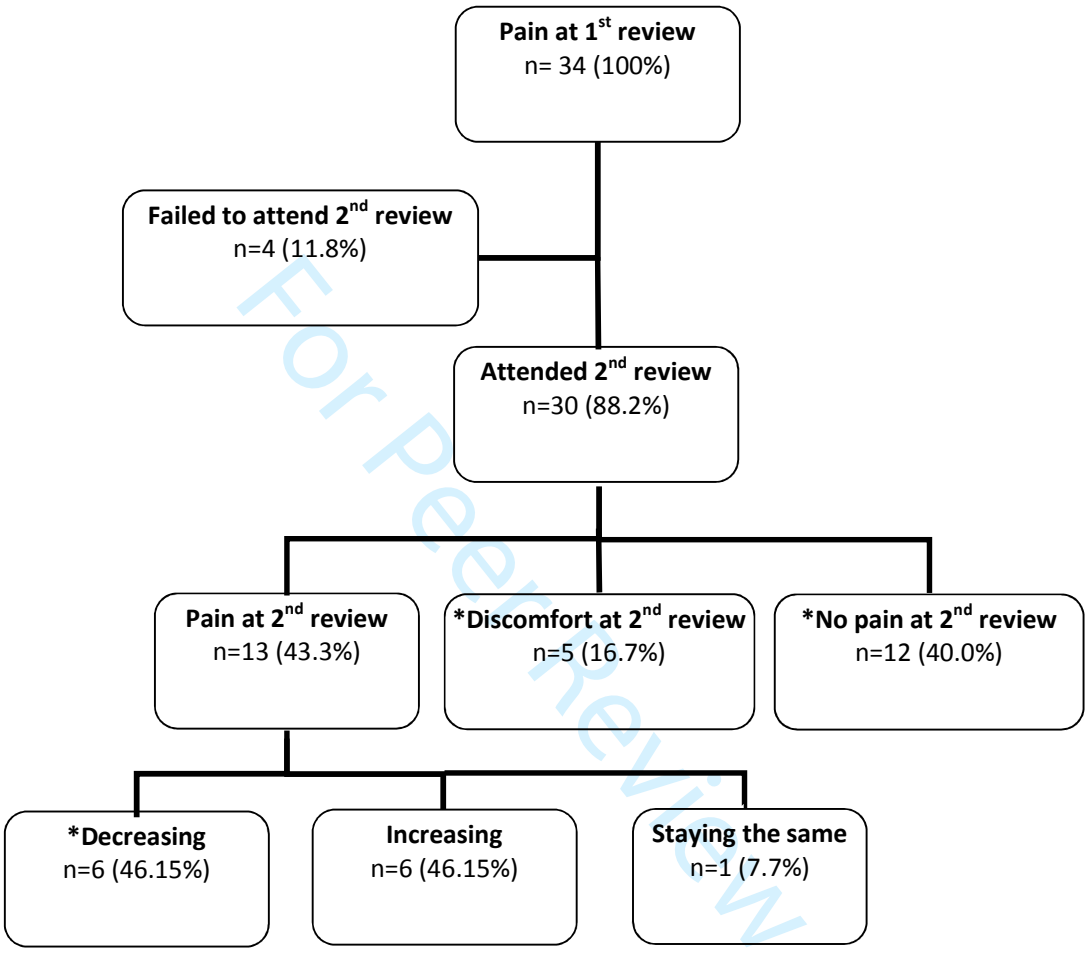
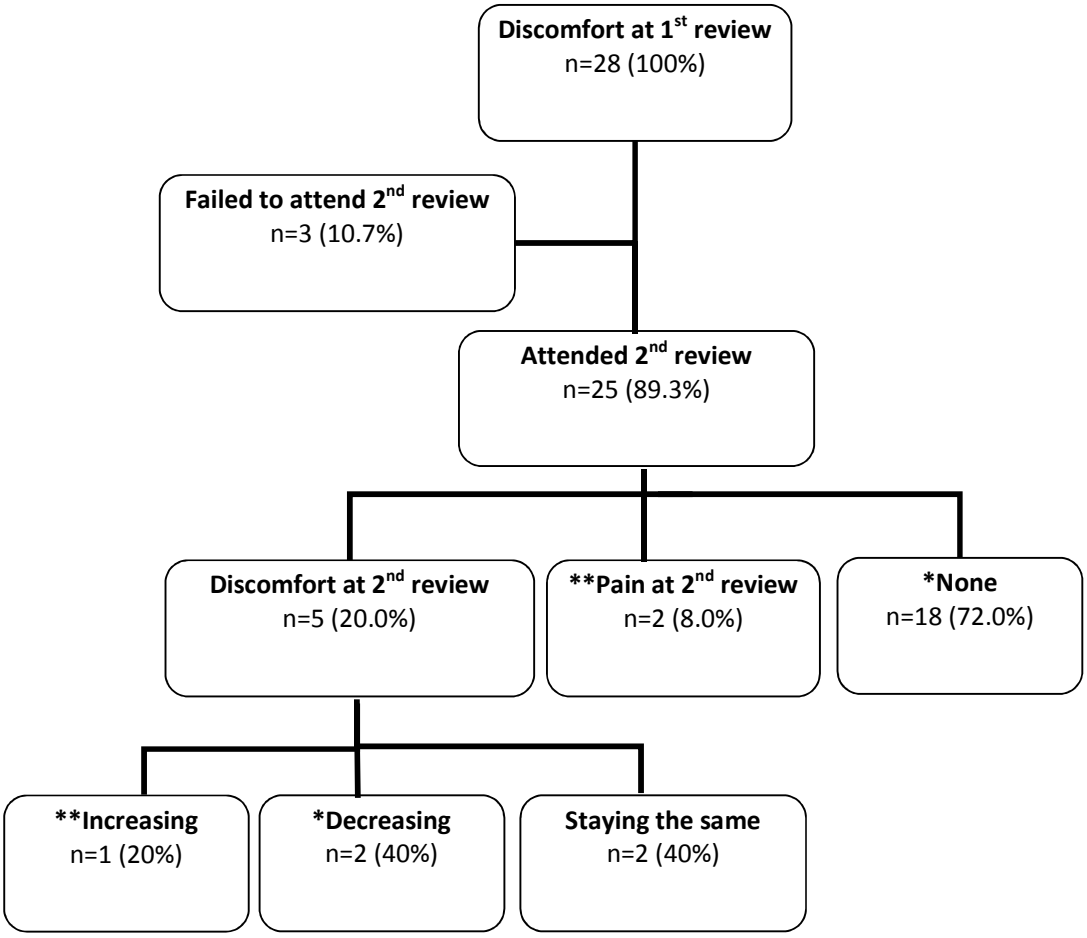


*Cases with pain intensity decreased or disappeared (n = 6+5+12 = 23)

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.



*Cases with discomfort disappeared or intensity reduced (n=18+2=20)
**Cases with discomfort became worse or pain (n=1+2=3)

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

	Complete	Incomplete	Failure	Uncertain	Total
			1st Review (n = 264)		
Pain	10 (15.4%)	24 (13.0%)	1 (9.1%)	2 (50.0%)	37 (14.0%)
Discomfort	6 (9.2%)	22 (12.0%)	1 (9.1%)	0 (0%)	29 (11.0%)
None	*49 (75.4%)	**138 (75.0%)	9 (81.8%)	2 (50.0%)	198 (75.0%)
Total	**65 (100%)**	**184 (100%)**	**11 (100%)**	**4 (100%)**	**264 (100%)**
			2nd Review (n = 55)		
Pain	6 (22.2%)	9 (34.6%)	-	-	15 (27.8%)
Discomfort	4 (14.8%)	6 (23.1%)	-	-	10 (18.5%)
None	18 (63.0%)	12 (42.3%)	-	-	30 (53.7%)
Total	**27 (100%)**	**26 (100%)**	-	-	**55 (100%)**

Pain = SF-MPQ pain VAS score > 0; discomfort = SF-MPQ pain VAS score = 0, plus individual descriptor score > 0
'-' = none of the cases were judged as failed or uncertain periapical healing outcome
*45 of the 49 cases attended further review (1-4 years) and all remained asymptomatic
**105 of the 138 cases attended further review (1-4 years) and all remained asymptomatic.

Table 23. Intensity of pain (based on the SFMPQ records) associated with teeth with periapical healing ("complete" or "incomplete") at the first review.

	Complete (n=10)		Incomplete (n=24)	
	Median	*Range*	*Median*	*Range*
VAS scores	3.4	1-6	2.9	0.6-6
VAS+Evaluative scores	4.9	2-8	4.4	1-8
SFMPQ descriptor total	7.9	1-22	6.1	1-30
Number of Words Chosen	4.9	1-10	3.6	1-13

Table 3. Multi-variable logistic regression models incorporating presence of pain/discomfort as the dependent variable, and "history of chronic pain" (Model 1), or "pre-operative pain" (Model 2), and simultaneously with another three significant explanatory variables (n = 249).

Explanatory variable	Odds ratio	95% Confidence Interval	*P* value
Model 1			
History of chronic pain			
No (*Reference*)	1		
Yes	3.50	1.45, 8.43	0.005
Pre-operative pulpal status			
Unresponsive (*Reference*)	1		
Responsive	5.23	1.51, 18.13	0.009
Pre-operative crack			
Absence (*Reference*)	1		
Presence	2.35	0.96, 5.75	0.06
Lesion size (mm)	0.87	0.78, 0.97	0.009
Model 2			
Pre-operative pain			
Absence (*Reference*)	1		
Presence	2.93	1.06, 8.11	0.04
Pre-operative pulpal status			
Unresponsive (*Reference*)	1		
Responsive	4.75	1.25, 18.07	0.02
Pre-operative crack			
Absence (*Reference*)	1		
Presence	2.51	1.00, 6.31	0.05
Lesion size (mm)	0.85	0.76, 0.95	0.005

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No.	Recommendation	Page No.	Relevant text from manuscript
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	Title page, abstract, page 2	This is an observational study indicated in the Title, Abstract aim, and the main manuscript
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	Abstract page	Provided in the abstract
Introduction				
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	3-4	
Objectives	3	State specific objectives, including any prespecified hypotheses	4	
Methods				
Study design	4	Present key elements of study design early in the paper	5-6	
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	3, 4	
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	5	Under sections with following titles: Ethical approval, inclusion & exclusion criteria
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case		
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	9 and appendix III	Under section: data management and analyses
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	*9*	Under section: data management and analyses
Bias	9	Describe any efforts to address potential sources of bias	7	Under section: Data

				management and analyses
Study size	10	Explain how the study size was arrived at	6	Under the section: Sample size estimation

Continued on next page

Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	9	Under section: Data management and analyses
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	9	Under section: Data management and analyses
		(*b*) Describe any methods used to examine subgroups and interactions	9	Under section: Data management and analyses
		(*c*) Explain how missing data were addressed	9	Under section: Data management and analyses
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	9	Under section: Data management and analyses
		(*e*) Describe any sensitivity analyses		
Results				
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	10	
		(b) Give reasons for non-participation at each stage	10	
		(c) Consider use of a flow diagram		
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	10	
		(b) Indicate number of participants with missing data for each variable of interest	None	
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	10	
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	10	
		Case-control study—Report numbers in each exposure category, or summary measures of exposure		
		Cross-sectional study—Report numbers of outcome events or summary measures		
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	Appendix III	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)
	(*b*) Report category boundaries when continuous variables were categorized	
	(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	

Continued on next page

Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	
Discussion			
Key results	18	Summarise key results with reference to study objectives	13-18
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	13
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	13-18
Generalisability	21	Discuss the generalisability (external validity) of the study results	13
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	N/A

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.