Frequency of Persistent Tooth Pain after Root Canal Therapy: A Systematic Review and Meta-Analysis

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Abstract

Introduction: Little is known about the frequency of persistent pain after endodontic procedures even though pain is a core patient-oriented outcome. We estimated the frequency of persistent pain, regardless of etiology, after endondontic treatment. **Methods:** Persistent tooth pain was defined as pain present ≥6 months after endodontic treatment. Endodontic procedures included in the review were pulpectomy, nonsurgical root canal treatment, surgical root canal treatment, and retreatment. Four databases were searched electronically complemented by hand searching. Two independent reviewers determined eligibility, abstracted data, and assessed study quality. A summary estimate of persistent all-cause tooth pain frequency was established by using a random-effects meta-analysis. Using subgroup analyses, we explored the influence of treatment approach (surgical/nonsurgical), longitudinal study design (prospective/retrospective), follow-up rate, follow-up duration, initial treatment versus retreatment, and quality of reporting (Strengthening the Reporting of Observational Studies in Epidemiology rankings) on the pain frequency estimate. **Results:** Of 770 articles retrieved and reviewed, 26 met inclusion criteria. A total of 5,777 teeth were enrolled, and 2,996 had follow-up information regarding pain status. We identified 168 teeth with pain and derived a frequency of 5.3% (95% confidence interval, 3.5%-7.2%, $p < 0.001$) for persistent all-cause tooth pain. High and statistically significant heterogeneity among studies (I^2 = 80%) was present. In subgroup analysis, prospective studies had a higher pain frequency (7.6%) than retrospectives studies did (0.9%). Quality of study reporting was identified as the most influential reason for study heterogeneity. **Conclusions:** The frequency of all-cause persistent tooth pain after endodontic procedures was estimated to be 5.3%, with higher report quality studies suggesting >7%. *(J Endod 2010;36:224–230)*

Key Words

Frequency, meta-analysis, outcome, pain, root canal therapy, systematic review

Tooth pain causes suffering and reduced functioning and is a major component of oral health and quality of life (1–3). Pain is often the motivation for an individual seeking dental care (4–6) although for some patients the fear and anxiety associated with dental pain prevents them from requesting needed care (7, 8). Acute postsurgical pain is known to cause functional changes in the nervous system (9), and research suggests that improved perioperative pain control can result in reduced chronic pain (10). Our overarching research goal is to better understand intraoral pain associated with dental procedures, with the long-term objective of being able to implement preemptive interventions to decrease postprocedural pain.

Customarily, research assessing the outcomes of root canal therapies has focused not on pain, but rather on the presence of radiographic signs, specifically periapical rarefaction (11–13). When this metric is used to define the success/failure of endodontic procedures, reports suggest an overall favorable outcome rate ranging from 68% to 91% after at least 1 year (14–17). The problem with using periapical rarefaction as the primary measure of outcome status, either alone or as part of a composite index, is that it fails to address the issues of primary concern to patients – whether it hurts and whether the patient can function (18–21). By definition, periapical rarefaction is a surrogate outcome measure, because the patient cannot perceive it (22). The use of surrogate outcomes can be misleading, at times resulting in unneeded treatment (23).

Following the principles of epidemiology and patient-centered care (24), better primary outcome measures for the success of endodontic treatment are a) retention of the tooth, b) absence of pain, c) adequate oral functioning, d) patient satisfaction, and e) adequate overall quality of life (21, 25). Tooth survival has been the focus of some studies of endodontic treatment (18, 26). Although the survival of teeth could be related to the absence of pain symptoms, tooth survival alone is not a definitive indication that patients are asymptomatic after treatment. The importance of evaluating the outcome of pain is all the more evident by the knowledge that pain is a prominent reason for tooth loss (27) and for continued care seeking (4, 5), is a major component of oral functioning (28), and is associated with long-term negative perceptions of dental care (29).

Pain at ≥6 months after root canal therapy (ie, persistent pain) is known to occur and has many possible explanations, including an untreated or incompletely obturated canal, failed coronal seal, tooth fracture, pain associated with an adjacent tooth, referred pain from a nonodontogenic structure, or deafferentation pain. Thus, such

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pain might best be characterized as all-cause pain. Whatever the underlying etiology, it is important for dentists to keep in mind that the subjective feeling of pain is the contributing negative factor for their patients.

Although persistent pain is an important outcome in dentistry, its frequency, severity, and extent of interference with daily life has not been well characterized in dental care populations. Adequate treatments for some of these pains are emerging, and early identification and treatment may improve prognosis (30), but the first step is to determine how widespread the problem is. To our knowledge, no individual study has systematically reviewed the endodontic literature to assess the frequency of persistent pain as a primary outcome. To fill this important knowledge gap, we conducted this systematic review of published endodontic treatment studies and performed a meta-analysis of their data to estimate the frequency of all-cause tooth pain at 6 months or greater in patients who underwent root canal therapy on permanent teeth. We also explored, through subgroup analyses, the influence of treatment approach, study design, follow-up rate, follow-up duration, initial treatment versus retreatment, and quality of reporting (Strengthening the Reporting of Observational Studies in Epidemiology [STROBE] rankings) on the pain frequency estimate.

Methods

Eligibility Criteria

Eligible for inclusion in this review were endodontic procedure articles that were published in any language up to June 5, 2009, and that reported on postoperative tooth pain at a minimum of a 6-month follow-up. The endodontic procedure could be initial treatment or retreatment and surgical or nonsurgical but not pulpotomy, partial pulpectomy, or pulp capping. The unit of observation was a human permanent tooth *in vivo*; primary teeth were excluded. The study outcome was the presence of all-cause pain; we did not differentiate among or exclude on the basis of pain etiologies. The outcome of all-cause tooth pain was considered positive if reported by either the patient or the practitioner. Pain could be spontaneous or provoked by biting, palpation, or percussion.

Inclusion of a study was dependent on having data to calculate the frequency of occurrence of postoperative pain; thus, if the count was not reported for the baseline population from which the follow-up sample was drawn, the article was excluded. This criterion resulted in the inclusion of cohort studies and clinical trials and the exclusion of case series, cross-sectional, and case-control studies. Articles reporting randomized controlled trials were included as a special type of prospective cohort study; however, the pain outcomes associated with individual treatment arms were combined given that our study outcome variable was all-cause pain. Unpublished research and studies that were reported only in abstract form were not considered for inclusion.

Information Sources and Search Strategy

We conducted an initial search in MEDLINE via the PubMed interface covering the period from 1949 to June 5, 2009, using the following search terms: pain OR quality of life OR hypersensitivit*) AND (root canal* OR endodont*) AND (cohort stud* OR prognos* OR treatment failure OR morbidity OR survival analysis OR disease susceptibility OR disease progression OR disease free survival OR time factor* OR recurrence OR clinical course OR inception cohort OR predict* OR outcome OR course OR postoperative OR longitudinal stud* OR treatment outcome OR follow-up stud* OR followup stud* OR prospective) NOT Review (publication type). This search was then adapted for use and run in the Cochrane Library, TRIP database, and Google Scholar. We assumed a priori that most data on the frequency of pain would come from studies that were not necessarily designed to assess pain as their primary outcome. Therefore, we also hand searched the references of prominent articles, literature reviews, and textbook chapters (source list available upon request). Our intent was to be broad in scope to ensure the inclusion of as much relevant existing data as reasonably possible.

Selection Process and Reliability Testing

Identified articles were screened by two of the authors (DRN and EJM) who were trained beforehand to apply the eligibility criteria. Training began with 10 randomly selected abstracts. This was followed by a calibration exercise in which the abstracts of 40 randomly selected articles were independently reviewed by the two raters and the results compared. Interrater agreement was found to be "substantial" (kappa = 0.79) according to published guidelines (31). Training and reliability testing was overseen by another author (MTJ).

If the information in the abstract and title was insufficient to determine eligibility, the article's full text was retrieved and reviewed. If the article was written in a language other than English, a person fluent in that language read the entire article in the presence of the raters who then assessed its eligibility. The raters met to compare their screening results for all articles, and disagreements were discussed until a consensus was reached. If the disagreement could not be resolved, arbitration was sought from two other dentists (MTJ on methodology and ASL on scientific content) whose decision was deemed final.

Data Abstraction and Study Variables

For all articles that met eligibility criteria, the full text was acquired electronically. Data abstraction forms were used by two independent reviewers (DRN and EJM) to obtain the following information: type of endodontic procedures, study design, stage of treatment (initial vs retreatment), use of nontraditional endodontic procedures (ie, N2 paste and external laser ablation of the root tip), number of teeth enrolled, number of teeth followed to 6 months or greater, number of teeth associated with pain, duration of follow-up, number of multiple observations per patient, and STROBE criteria (Table 1). Any differences in the abstraction reports were resolved in the same manner as outlined earlier for the article selection process.

Two articles (32, 33) did not clearly state that only one tooth was treated in each of the enrolled patients. We made the assumption that each tooth came from a separate participant. This is a reasonable assumption given the implied wording of the reports and the low overall frequency (1.2%) of multiple treatments in patients from the final set of articles.

Assessment of Study Quality by Reporting

We used the STROBE criteria (34) to assess the quality of study reporting. A total of 22 criteria pertaining to the title, abstract, introduction, methods, results, or discussion were assessed as either met or not met. Each item was given equal weight (a single point if met). Thus, the possible range of quality summary scores was 0 to 22. We divided studies into lower and higher reporting quality by using a median split of the quality summary scores.

Statistical Methods

We used the random-effects method for meta-regression (35) to determine a summary estimate for frequency of all-cause pain at $\geq$6 months after endodontic treatment. In a sensitivity analysis, we examined whether the deletion of a single study would substantially change the meta-analysis summary estimates. To explore factors influencing the estimates, we performed subgroup meta-analyses for each category of the following variables: i) surgical versus nonsurgical treatment,

TABLE 1. Characteristics of the 26 Studies Included in the Meta-analysis

Authors, year	Endodontic procedure	Study design	Teeth enrolled	Follow up rate (%)	All-cause tooth pain	Multiple procedures	Follow-up (years)	STROBE rating
Altonen & Mattila, 1976*	Periapical Surgery	Retrospective	64	72	**3**	0	1–6	9.8
Christiansen et al, 2009	Periapical Surgery	Prospective	52	89	**3**	8	1–1	18
Danin et al, 1999*	Periapical Surgery	Prospective	10	100	**0**	0	1–1	10.7
de Chevigny et al, 2008a*	Initial NSRCT	Prospective	582	24	**8**	71	4–6	20.5
de Chevigny et al, 2008b*	Re-Treatment NSRCT	Prospective	477	26	**8**	94	4–6	20.5
De Moor & De Witte, 2002	Initial NSRCT	Retrospective	12	100	**0**	1	1.5–8	4.9
Dietrich et al, 2003*	Periapical surgery	Undetermined	25	92	**2**	1	0.5–1	10.1
Farzaneh et al, 2004a*	Re-Treatment NSRCT	Prospective	523	20	**7**	79	4–6	20.5
Farzaneh et al, 2004b*	Initial NSRCT	Prospective	442	28	**7**	71	4–6	20.5
Gao et al, 2000	Initial NSRCT	Prospective	270	70	**38**	19	0.5–4	15.5
Gesi et al, 2006	Initial NSRCT	Prospective	256	93	**10**	0	0.5–3	21
Hession, 1981*	Initial NSRCT	Retrospective	105	100	**2**	0	0.5–20	0
Ioannides & Borstlap, 1983*	Periapical Surgery	Retrospective	86	81	**1**	0	0.5–5	6.5
Koba et al, 1999	Initial NSRCT	Prospective	44	100	**3**	6	0.5-0.5	8
Liu & Sidhu, 1995	Initial NSRCT	Prospective	6	100	**0**	0	1–3.5	5
Lyons et al, 1995*	Periapical Surgery	Retrospective	200	49	**0**	0	5–5	7
Marquis et al, 2006*	Initial NSRCT	Prospective	532	25	**10**	64	4–6	19.5
Negm, 1983	Initial NSRCT	Prospective	116	94	**3**	0	1.5–2	2
Pekruhn, 1986	Combined Treatments	Retrospective	1140	81	**9**	222	1–1	3.3
Polycarpou et al, 2005	Combined Treatments	Prospective	400†	44	**37**	0	1–1	20
Seto et al, 1985*	Unreported	Prospective	46	100	**3**	30	0.5–9	2.7
Shearer et al, 2008	Periapical surgery	Prospective	50	94	**3**	0	0.5–0.5	1.5
Van Doorne et al, 1996	Combined Treatments	Prospective	62	53	**9**	12	0.5-1.5	6.5
von Arx et al, 2001*	Periapical Surgery	Prospective	26	96	**1**	1	1–1	9
von Arx & Kurt, 1999	Periapical Surgery	Prospective	50	86	**1**	7	1–1	8
Werts, 1975*	Unreported	Retrospective	201†	45	**0**	0	1–2	0
	Aggregate values		5,777	52	168	686	0.5–20	8.5

NSRCT = non-surgical root canal therapy.

*Reference found by hand searching.

†Assumed that each patient contributed only 1 tooth.

ii) prospective versus retrospective study design, iii) follow-up rate of recall, iv) follow-up at 6 to 12 months versus greater than 12 months, v) initial treatment versus retreatment, and (vi) quality of reporting. If data were missing or unclearly reported in the article, the study was omitted from the analysis for this particular variable.

All analyses were performed by using the statistical software package STATA (Stata Statistical Software: Release 10.1; StataCorp LP, College Station, TX) and the user-written metan commands.

Results

Study Identification and Characteristics

From our search strategy, we identified 770 articles (495 by electronic searching of databases and 275 by hand searching), the oldest being published in 1921. Twenty-eight were published in a language other than English (7 French; 6 Chinese; 5 Japanese; 2 each in Italian, Russian, and Spanish; and 1 each in Croatian, Danish, German, and Greek). Screening of the titles and abstracts resulted in 307 articles being excluded. After full text review, another 437 articles were excluded, resulting in 26 articles for inclusion in the meta-analysis (Fig. 1). Twenty-four of these were published in English, 1 in French, and 1 in Chinese.

Examples of some of the most common reasons why articles were excluded are as follows: a) unclear reporting resulting in the inability to link outcome of pain with individual case status (eg, Nord, 1970; Van Hieuwenhuysen et al, 1994; Lobb et al, 1996; and Friedman et al, 2003); b) follow-up time either less than 6 months (eg, Seltzer et al, 1961), not specified (eg, Marbach et al, 1982), or presented as an aggregate (eg, Campbell et al, 1990); c) combined/composite outcome measure with the inability to determine individual case status

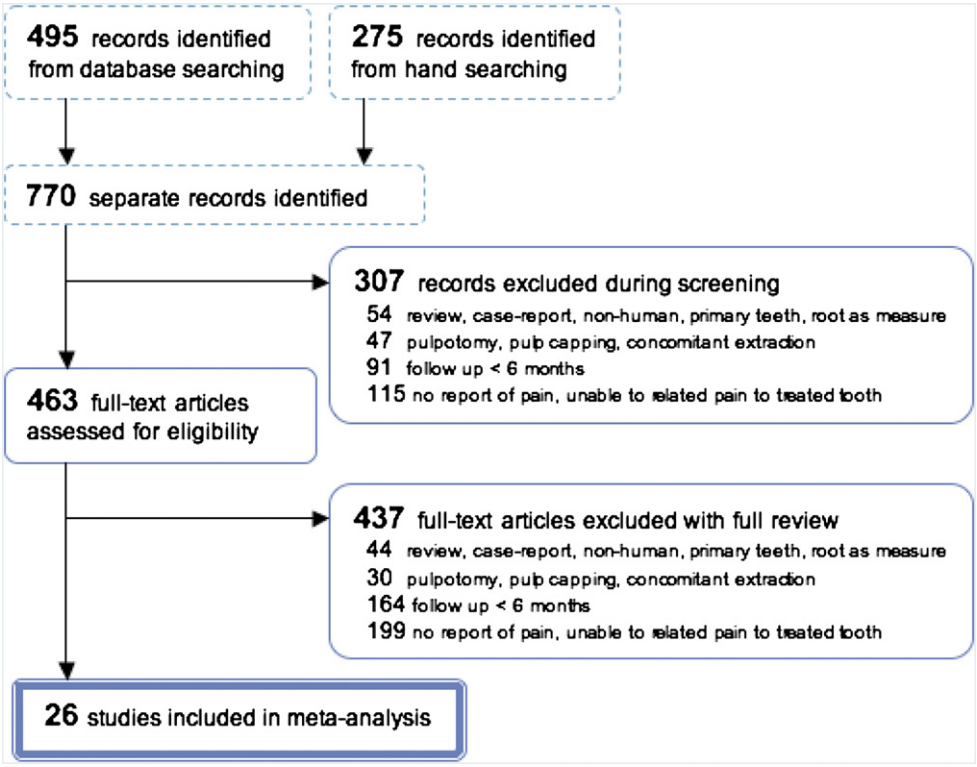

Figure 1. Flowchart of the systematic review process.

(eg, Tjäderhone et al, 1995; Ørstavik, 1996; Wang et al, 2004; and von Arx et al, 2007); d) confounding because of concomitant tissue injury (eg, Nethander, 1998; and Fuks et al, 1993); e) unit of observation reported as an individual tooth root instead of a single tooth (eg, Friedman et al, 1995; and Abramovitz et al, 2002); f) cross-sectional design with no time of follow-up information (eg, Allad and Palmqvist, 1986; and Lin et al, 1991); g) number of subjects in the original cohort from which the sample was drawn was not reported (eg, Block et al, 1985; Grötz et al, 1998; and Llena-Puy et al, 2001); h) pain at follow-up time was not assessed (eg, Bender et al, 1964; Rud et al, 1972; Dugas et al, 2003; and Boykin et al, 2003); i) report was a literature review (eg, Kojima et al, 2006); and j) case report, case series, or other preselected study samples that did not represent the population from which the study samples were drawn (eg, Tidwell et al, 1999; Boucher et al, 2000; and Brynjulfsen et al, 2002).

The 26 studies that were included differed in the types of endodontic treatments provided, number of teeth treated (6-1,140), duration of follow-up (0.5-20 years), and percentage of teeth followed up (24%-100%) (Table 1). From 5,777 teeth enrolled in the 26 studies, 2,996 teeth were followed up after at least 6 months. Among them, 168 teeth (5.6%) presented all-cause pain. Five of the 26 studies reported no cases of persistent pain. Variation in the quality of reporting was observed. The median reporting quality score (STROBE rating) was 8.5 (interquartile range = 4.9-19.5, range = 0-22).

Summary Estimate of Pain Frequency

The computed summary estimate for frequency of persistent, all-cause pain occurrence over the 26 studies was 5.3% (95% confidence interval, 3.5%-7.2%; $p < 0.001$; Fig. 2). "High" heterogeneity (ie, inconsistency) (36) among study estimates was observed ($I^2 = 80\%$, $p < 0.001$). When each study was eliminated in turn from the analysis and the primary analysis was run with the remaining studies, the overall frequencies for the 26 separately run analyses ranged from 4.5% to 5.8%. These results indicate that individual studies did not unduly influence the summary estimate.

Exploration of Study Heterogeneity

In subgroup analyses, reporting quality (as assessed by the STROBE rating) was the strongest factor influencing pain frequency; the subgroup analysis revealed that the upper half of the studies had the highest frequency of persistent pain (Table 2). Studies with reporting quality scores above the median had a pain frequency of 8.3%, whereas studies with reporting quality scores below the median had a pain frequency of 1.4%. The single most influential study characteristic was longitudinal design, which was strongly correlated with study report quality (tetrachoric correlation coefficient = 0.68). Retrospective studies had the lowest estimate of pain frequency (0.9%), whereas prospective studies had the second-highest estimate (7.6%).

Discussion

This broadly inclusive systematic review identified 26 studies (2,996 enrolled teeth) that reported participants' pain status, regardless of etiology, at 6 months or later after root canal treatment. Across studies, the summary estimate of all-cause persistent pain was 5.3%. This finding, combined with the knowledge that more than 16.4 million root canals are performed annually in the United States (37), suggests that approximately 875,000 endodontic patients experience persistent pain every year. The psychosocial distress related to such pain is known to result in dental anxiety and fear (38), which, in turn, is a major barrier for dental care (4, 39–41) and can lead to other negative psychosocial consequences (7). In this context, the estimated frequency of persistent pain associated with endodontic procedures is not trivial. Such pain contributes to the individual and societal burden

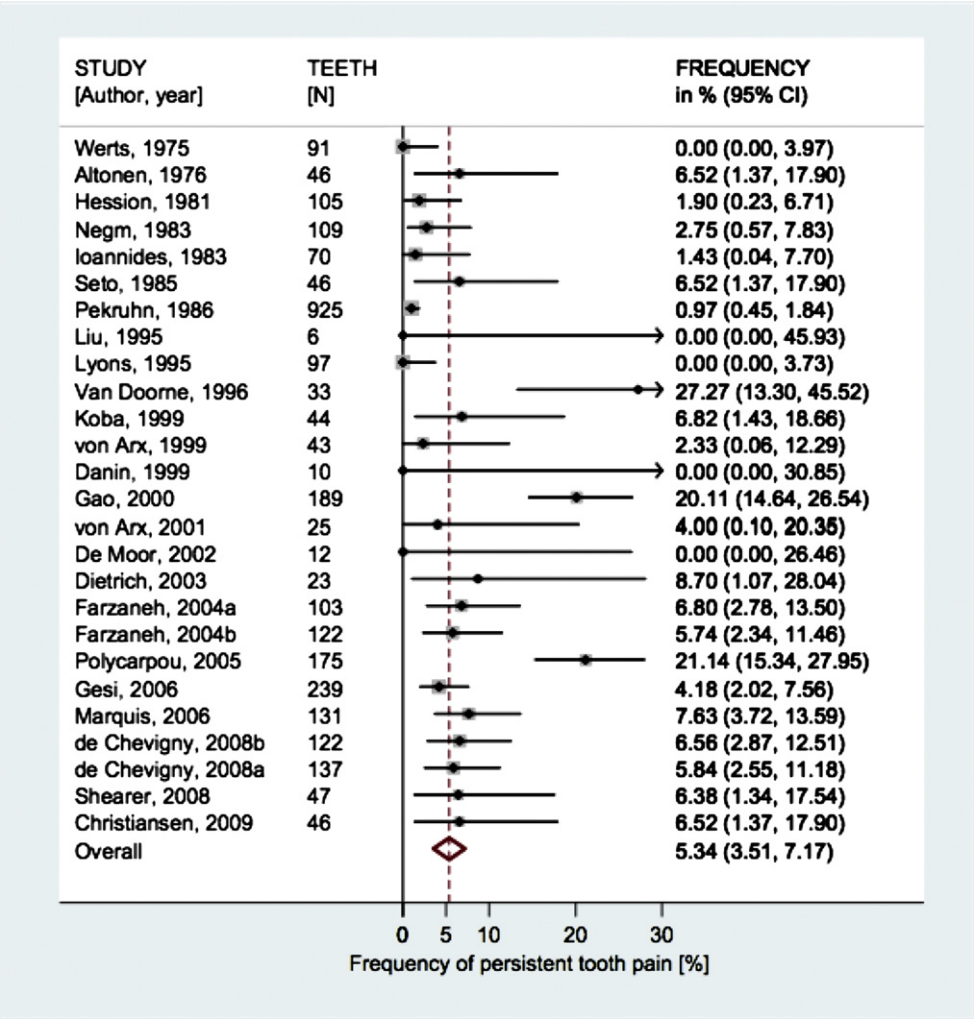

Figure 2. Random effects meta-analysis of the frequency of all-cause persistent tooth pain in 26 studies.

caused by chronic tooth pain and may be considered a significant public health issue.

Our inclusion criteria and search strategy resulted in the abstraction of data from articles not normally used to describe the association between persistent pain and root canal therapy. Two articles that were published in non-English languages (42, 43) contributed 272 teeth, with 28% (47/168) of persistent tooth pain cases. Conversely, two articles (44, 45) that are often cited to support the existence of persistent postendodontic pain and related topics were not included in this meta-analysis because the duration of follow-up of both cases and controls could not be unequivocally determined to be 6 months or greater. Fourteen articles (32, 46–58) were identified from hand searching. These articles contributed 1,128 teeth and 52 cases of tooth pain. Our findings suggest that hand searching and the inclusion of non-English literature is important in a comprehensive review of the literature, as previously suggested (59, 60).

Even if a comprehensive review is performed, meta-analytical reviews are limited by the strength and rigor of the individual studies that are included in the statistical summary (61, 62). We found that studies with above-the-median STROBE scores, which is a measure of the quality of study reporting, had a frequency of persistent pain (8.3%) greater than that of lower-quality studies (1.4%). The most influential single study characteristic among those evaluated was the longitudinal study design. Prospectively designed studies are thought to provide more accurate estimates of the outcome of interest (63). In addition, measures that are the primary outcome of a study tend to yield more accurate estimates than those associated with reports of secondary findings such as side effects (64). Of the 26 articles in our review and meta-analysis, only one was designed to assess pain as the primary outcome measure (33). Notably, the reported frequency of occurrence of all-cause tooth pain in that study was 21%.

Besides longitudinal study design, we considered loss to follow-up to be important. This study characteristic has been repeatedly shown to lower the frequency of occurrence in observational studies (65) because patients with problems associated with their care, such as pain, are more apt not to follow up with the same care provider (66). Within our meta-analysis, the average loss-to-follow-up rate across all included studies was very high, 48%, and may therefore have a potential for the introduction of bias (67); however, our subgroup analyses did not find substantial differences between two categories of patient attrition. Another important methodologic factor for our endodontic studies was the failure to report on the follow-up pain status of teeth that were extracted (48, 49, 51, 52). This makes it difficult to conclude whether or not the outcome of interest occurred before the loss of the tooth. Because some teeth may have been extracted because of pain, it is possible that some studies systematically

TABLE 2. Assessment of Study Heterogeneity by Subgroup Analysis

Study Characteristics Assessed	Number of studies (%) with Characteristic	Pain Frequency Estimate (95% confidence interval)	P value
Treatment approach[#]	15 (63) Non-surgical	7.2 (4.2-10.2)	<0.001
	9 (38) Surgical	1.2 (-0.3-2.7)	0.117
Longitudinal study design*	7 (28) Retrospective	0.9 (0.3-1.5)	0.005
	18 (72) Prospective	7.6 (5.0-10.3)	<0.001
Follow-up rate	8 (31) <50%	6.2 (2.4-9.9)	0.001
	18 (69) ≥50%	5.0 (2.7-7.4)	<0.001
Follow-up length	9 (35) 6-12 months	6.5 (1.3-11.6)	0.014
	17 (65) >12 months	5.1 (2.8-7.3)	<0.001
Treatment stage	20 (77) Initial treatment	6.0 (3.0-9.1)	<0.001
	6 (23) Retreatment	6.6 (3.4-9.9)	<0.001
Reported study quality (STROBE)	13 (50) Lower half	1.4 (0.2-2.7)	0.022
	13 (50) Upper half	8.3 (5.2-11.5)	<0.001

[#]Two studies with missing data.

*One study with missing data.

excluded painful teeth. We were not able to investigate this bias, but it would likely lead to an underestimation of the true frequency of the occurrence of all-cause pain among teeth that remained at follow-up.

In our exploratory subgroup analyses, surgical procedures were related to a lower pain frequency. This seems counterintuitive because more invasive procedures are thought to lead to more severe pain outcomes (10). We also observed no difference between the 6 studies that used experimental procedures (Koba et al, 1999: YAG laser; Lui and Sidhu, 1995: enrolled only cracked teeth; Negm, 1983: silver percha cones; Seto et al, 1985: exposed to ionizing radiation; Van Doorme et al, 1996: CO_2 laser; and Werts, 1975: Sargenti technique) and those using typical endodontic techniques and patients, also not what would be expected. These results may be explained because of varying study designs (ie, retrospective), small numbers of patients (ie, <100 patients), and publication bias. Further subgroup analysis revealed that pain frequency did not substantially differ by treatment stage, suggesting that the outcome of persistent pain is equally likely after both types of intervention. Similarly, we did not find a substantial difference in the persistent pain frequency for studies with greater than a 12-month follow-up and studies with a 6- to 12-month follow-up, indicating that pain present within the first year after root canal therapy can persist for years into the future. Because of the high levels of heterogeneity present within these analyzed studies and the low statistical power with such tests, caution needs to be used when drawing conclusions from subgroup analysis data.

Our study has some limitations. A methodologic challenge of our review was that the reporting unit was the tooth, whereas the outcome of persistent pain is a patient-based measure. The tooth happens to be the unit most often used in the endodontic literature, but this choice means that one person could have more than one root canal procedure being counted. The teeth counted within the same individual do not represent statistically independent observations because they share the same environment. Our persistent tooth pain frequency estimate would not be affected by correlated data, but the width of the confidence interval around our estimate may be too narrow. However, we believe that correlated data are not likely a major source of bias because even though 15 studies reported multiple observations per patient, the difference between the number of patients and the total number of teeth was small (1.2%, 686/5777). Conceptually more challenging is the limitation that the studies were mainly performed in university-based settings or tertiary care centers. Usually, these settings result in an increase in the estimate of unfavorable health care outcomes because is it thought that more difficult patients are seen in these environments (68). On the other hand, clinicians in these centers may be more experienced with these procedures and thus produce better outcomes. Therefore, how far our results generalize to the general practice setting is not known.

In conclusion, our estimate of the frequency of all-cause tooth pain at 6 months or longer after root canal therapy of permanent teeth is approximately 5%. Higher persistent pain estimates (>7%) were derived for studies with a higher quality of reporting score and studies that used a prospective (versus retrospective) design. Given this, our estimates likely reflect a lower limit of chronic pain frequency after endodontic procedures. Future studies that are more methodologically rigorous would be beneficial for refining the magnitude of persistent pain frequency. A precise and generalizable estimate of the occurrence of persistent tooth pain after root canal therapy as well as an evaluation of its effects and a determination of risk factors would be beneficial to both patients and providers. Such knowledge could influence decisions about dental treatment and facilitate the development of preventative treatment strategies.

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