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REVIEW

The prevalence of postoperative pain and flare-up in single- and multiple-visit endodontic treatment: a systematic review

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Abstract

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Aim The aim of this systematic review was to assess the evidence regarding postoperative pain and flare-up of single- or multiple-visit root canal treatment.

Methodology CENTRAL, MEDLINE and EMBASE databases were searched. Reference lists from identified articles were scanned. A forward search was undertaken on the authors of the identified articles. Papers that had cited these articles were also identified through Science Citation Index to identify potentially relevant subsequent primary research.

Review methods The included clinical studies compared the prevalence/severity of postoperative pain or flare-up in single- and multiple-visit root canal treatment. Data in those studies were extracted independently.

Results Sixteen studies fitted the inclusion criteria in the review, with sample size varying from 60 to 1012 cases. The prevalence of postoperative pain ranged from 3% to 58%. The heterogeneity amongst included studies was far too great to conduct meta-analysis and yield meaningful results.

Conclusion Compelling evidence indicating a significantly different prevalence of postoperative pain/flare-up of either single- or multiple-visit root canal treatment is lacking.

Keywords: comparison, post-treatment pain, treatment modalities.

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Introduction

Single- versus multiple-visit root canal treatment has been the subject of long-standing debate in the endodontic community (Bergenholtz & Spångberg 2004). In fact, the attempt to complete root canal treatment in one visit has been documented since the end of the nineteenth century (Dodge 1887), yet we have not come to a definitive conclusion. Some of the unresolved issues include differences in clinical outcomes, inadequate microbiological control and pain. This controversy can be investigated more systematically with the aid of an evidence-based approach. When clinicians are faced with choices of which treatment should be offered to patients, the central issues that should be considered are effectiveness, complications, cost (Sackett 2000) and probably patient/operator satisfaction. It has been established that the current best available evidence has failed to demonstrate a difference in therapeutic efficacy (healing rates) between these two treatment regimens in teeth with necrotic pulps and apical periodontitis (Sathorn *et al.* 2005). Complications of these two treatment approaches, though, have not yet been studied systematically.

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Pain and swelling are often indicators of an existing disease process associated with an offending tooth. Endodontic treatment aims to reverse the disease process and thereby eliminate the associated signs and symptoms. When the treatment itself appears to initiate the onset of pain and/or swelling, the result can be very distressing to both the patient and the operator. Patients might even consider postoperative pain and flare-up as a benchmark against which the clinician's skills are measured. Prevalence of postoperative pain or flare-up is, therefore, one of the influencing factors when making a clinical decision. Obviously, the treatment with the lower prevalence of postoperative pain is usually the treatment of choice as long as effectiveness and cost are not compromised. Even though postoperative pain in endodontics is not a particularly good outcome measure because it tends to be transient, it has been widely used as an argument either for or against single-visit root canal treatment. A majority of endodontists in the United States 25 years ago believed that there would be more pain if treatment was completed in one appointment (Calhoun & Landers 1982). Clinical decision making, however, should be based on the best clinical evidence rather than consensus.

This study aimed to address two clinical questions, which were constructed in PICO format [problem (P), intervention (I), comparison (C) and outcome (O)] as follows (Glasziou 2001):

(1) In patients undergoing root canal treatment, does a single-visit approach, compared to a multiple-visit approach, result in a higher frequency and/or severity of postoperative pain, as measured by the degree of pain reported by patients?

(2) In patients undergoing root canal treatment, does a single-visit approach, compared to a multiple-visit approach, result in a higher prevalence of flare-up, as measured by the number of patients returning to the practice and receiving active treatment to manage symptoms?

Postoperative pain is defined as pain of any degree that occurs after the initiation of root canal treatment, whilst endodontic flare-up has been defined as the onset or continuation of pain and/or swelling after endodontic treatment which is of such severity that it disrupts the patient's lifestyle enough that the patient requires an unscheduled appointment at which active treatment is undertaken (Walton & Fouad 1992). In other words, flare-up is a subset of postoperative pain representing a high degree of pain which is disruptive to the patient's routine.

Materials and methods

Literature search

An exhaustive search was undertaken to identify all clinical studies that compared the frequency/severity of pain and flare-up rate of single- and multiple-visit root canal treatment. The MEDLINE database was searched via the EviDents search engine (http://medinformatics.uthscsa.edu/EviDents/ last accessed: January 2007) using 'postoperative pain' and 'flare-up' as keywords, which automatically created a complex search strategy (Table 1). The same search strategy was also applied using CENTRAL and EMBASE databases. This complex search strategy was similar to the one recommended by the Cochrane Collaboration as outlined in the Cochrane Reviewers' Handbook (Higgins & Green 2005). The search of the MEDLINE database included all years from 1966 to January 2007. A similar search was undertaken on EMBASE (1988–2007). In addition, a thorough search of six thesis databases (*The Networked Digital Library of Theses and Dissertations, The Proquest Digital Dissertations, OAIster, Index to Theses, The Australian Digital Thesis Program and Dissertation.com*) and one conference report database (*BIOSIS Previews*®) was undertaken in an attempt to retrieve unpublished data. No language restriction was applied to the search. A total of 220 studies were subjected to the preliminary analysis. Titles and abstracts, where available, were scanned and the relevance of each study to pain and flare-up rate was determined. Where information from the title and abstract was not adequate in determining the paper's relevance, the paper was automatically included in subsequent analysis. A total of 200 studies were excluded from the list, and the 20 remaining articles were subjected to stricter exclusion criteria.

Table 1 Search strategy automatically formulated by EviDents search engine to find studies that compared postoperative pain and flare-up rates of single- and multiple-visit root canal treatment

No.	Search history	Results
1	Postoperative pain OR flare-up OR postoperative pain OR flare-up AND [endodontics (MeSH) OR apicoectomy (MeSH) OR pulpectomy (MeSH) OR pulpotomy (MeSH) OR root canal therapy (MeSH) OR root canal filling materials (MeSH) OR dental pulp test (MeSH) OR dental pulp diseases (MeSH) OR periapical abscess (MeSH)] NOT [animals (MeSH terms : noexp) NOT human (MeSH)]	220

MeSH, medical subject headings.

Inclusion and exclusion

The full texts of the remaining papers were then obtained and reviewed, and the inclusion criteria (Table 2) were applied. Seven papers (Pekruhn 1986, Friedman *et al.* 1995, Soares & Cesar 2001, DiRenzo *et al.* 2002, Siqueira *et al.* 2002, Oginni & Udoye 2004, Ghoddusi *et al.* 2006) were excluded for various reasons (Table 3). Reference lists from identified articles were scanned to identify other potentially relevant preceding articles (i.e. a backward search). Three more articles were identified (O'Keefe 1976, Soltanoff 1978, Mulhern *et al.* 1982). A forward search was undertaken on the authors of the identified articles. Papers that had cited these articles were also identified through the Science Citation Index (www.isinet.com), to identify potentially relevant subsequent primary research (Glasziou 2001).

Data extraction

A systematic data extraction sheet was constructed. All aspects of treatment that could potentially affect the study outcomes were identified and included in the data sheet. The data in all included studies were extracted in the same fashion.

Table 2 Inclusion and exclusion criteria used in the analysis

Inclusion criteria
Subjects had a non-contributory medical history
Subjects underwent non-surgical root canal treatment during the study
There was comparison between single- and multiple-visit root canal treatment
Outcome was measured in terms of pain degree or prevalence of flare-up
Exclusion criteria
Pain was not measured at the completion of the treatment
No comparison between single- and multiple-visit root canal treatment within the same study
No data regarding prevalence of pain or flare-up
No explicit details of endodontic clinical procedures

Table 3 Studies excluded from systematic review

Excluded studies	Exclusion criteria (see Table 2)
Pekruhn (1986)	3
Friedman *et al.* (1995)	3
Soares & Cesar (2001)	2
DiRenzo *et al.* (2002)	1
Siqueira *et al.* (2002)	2
Ghoddusi *et al.* (2006)	4
Oginni & Udoye (2004)	4

Results

Data summary of included studies

Sixteen studies were included in the analysis (Table 4). Sample size ranged from 60 to 1012 teeth. None of the studies justified the sample size selection. The majority of the studies did not differentiate preoperative pulpal/periapical status; preoperative pain was not reported either, despite its predictive value for postoperative pain (Torabinejad *et al.* 1988, Walton & Fouad 1992, Imura & Zuolo 1995, Mattscheck *et al.* 2001). Amongst the included studies, six were randomized controlled trials comparing single- and multiple-visit approaches directly, seven were prospective cohort studies, two were retrospective cohort studies and the details of one cohort study were inadequate to determine whether it was prospective or retrospective. In the cohort studies, single- and multiple-visit approaches were not compared directly, but rather constituted one of several factors that had been investigated.

Endodontic treatment procedures varied amongst studies in type of instrumentation technique, medication and concentration of sodium hypochlorite used as irrigant. Overall, the clinical procedures followed currently accepted standards, with the following variations: (i) Albashaireh & Alnegrish (1998), Imura & Zuolo (1995), Mulhern *et al.* (1982) and Walton & Fouad (1992) left canals empty between appointments; (ii) Eleazer & Eleazer (1998), Fava (1989) and Pekruhn (1981) used metacresylacetate, camphorated parachlorophenol (CMCP) and formocresol as intracanal medication, respectively; (iii) Fava (1994) and Soltanoff (1978) used anionic detergent and normal saline as irrigants, respectively. Sodium hypochlorite was used as an irrigant with concentration ranging between 0.5% and 5.25%. However, effects of different NaOCl concentrations on postoperative pain have not been demonstrated. Only one study has shown an effect of intracanal medication (corticosteroid) on postoperative pain, with no difference between calcium hydroxide and an empty canal (Ehrmann *et al.* 2003). Calcium hydroxide was used exclusively only in Al-Negrish & Habahbeh (2006), Fava (1994) and Gesi *et al.* (2006).

Outcome measures

Dichotomous outcome (i.e. 'yes' or 'no') was used in one postoperative pain study and four flare-up studies. The remaining studies used four-, five- or

Table 4 Result summary of included studies

	Design	PA status	Sample size	Medication	Outcome measure	Raw data pain/total (S versus M)	Statistical result
Eleazer & Eleazer 1998)	Retrospective cohort	AP present	402	Metacresylacetate	Flare-up	6/201 vs. 16/201	$P = 0.03$
Ng *et al.* (2004)	Prospective cohort	AP present	405	Various medication	Postoperative pain	53/91 vs. 113/324	$P < 0.001$
Fava (1994)	Prospective cohort	AP absent	60	Calcium hydroxide	Postoperative pain	2/30 vs. 1/30	NS
Al-Negrish & Habahbeh (2006)	RCT	AP absent	112	Calcium hydroxide	Postoperative pain	Not dichotomised	NS
Gesi *et al.* (2006)	RCT	AP absent	256	Calcium hydroxide	Postoperative pain	16/130 vs. 9/126	NS
O'Keefe (1976)	Prospective cohort	Mixed	132	Various medication	Postoperative pain	1/55 vs. 7/77	NS
Soltanoff (1978)	Retrospective cohort	Mixed	281	Not stated	Postoperative pain	17/88 vs. 27/193	NS
Pekruhn (1981)	RCT	Not stated	102	Formocresol	Postoperative pain	11/51 vs. 5/51	NS
Mulhern *et al.* (1982)	RCT	Not stated	60	No medication	Postoperative pain	8/30 vs. 12/30	NS
Oliet (1983)	Cohort[a]	Not stated	387	Not stated	Postoperative pain	28/236 vs. 8/115	NS
Roane *et al.* (1983)	Prospective cohort	Mixed	359	Not stated	Postoperative pain	38/250 vs. 34/109	$P = 0.001$
Fava (1989)	Prospective cohort	Not stated	60	CMCP	Postoperative pain	1/30 vs. 0/30	NS
Walton & Fouad (1992)	Prospective cohort	Mixed	935	No medication	Flare-up	5/196 vs. 24/739	NS
Imura & Zuolo (1995)	Prospective cohort	Mixed	1012	No medication	Flare-up	3/582 vs. 13/430	$P = 0.002$
Albashaireh & Alnegrish (1998)	RCT	Mixed	291	No medication	Postoperative pain	39/142 vs. 56/149	NS
Yoldas *et al.* (2004) Retreatment study	RCT	Mixed	227	Calcium hydroxide + CHX	Flare-up	8/106 vs. 2/112	$P = 0.05$

AP, apical periodontitis; CHX, chlorhexidine; NS, not statistically significant difference; RCT, randomised controlled clinical trial.
[a]Not known whether prospective or retrospective.

eight-point pain scales (e.g. no, slight, moderate and severe pain); however raw data were eventually combined and dichotomized to facilitate statistical analysis. The time at which pain was measured varied from 6 h to 30 days, with different recording frequency. Most studies reported measurement at 48 h. For the purposes of this analysis, postoperative pain and flare-ups were considered together. The measures were too variable to combine data for meta-analysis.

Study categorization

The presence of apical periodontitis is usually regarded as a confirmation of root canal infection (Sundqvist 1976, Law & Messer 2004, Sathorn *et al.* 2007). Also, the presence or absence of a periapical lesion has been used as a differentiating factor in the decision to treat in single or multiple visits (Spångberg 2001, Trope & Bergenholtz 2002). Thus, the 16 included studies were categorized according to periapical status in an attempt to correlate the data with other comparisons of single- versus multiple-visit treatment (such as healing).

Apical periodontitis present

Two studies were available in this category; one prospective cohort (Ng *et al.* 2004) and one retrospective cohort (Eleazer & Eleazer 1998). Prevalence of postoperative pain was significantly higher in single-visit root canal treatment in Ng *et al.* (2004) (P-value < 0.001). The odds of postoperative pain occurring in association with single-visit root canal treatment were 2.8 times that of multiple-visit treatment (odds ratio = 2.8; 95% CI: 1.7–4.7). Eleazer & Eleazer (1998) reported opposite results using flare-up rate as an outcome measure. Prevalence of flare-up was significantly higher in a multiple-visit approach (P-value = 0.03; Pearson uncorrected chi square; odds ratio = 2.8; 95% CI: 1.1–7.1).

Apical periodontitis absent

Three studies were available in this group; two randomized controlled trials (Al-Negrish & Habahbeh 2006, Gesi *et al.* 2006) and one prospective cohort study (Fava 1994). Postoperative pain was not significantly different between single- and multiple visit root canal treatment in these studies (P-value = 0.23, 0.16 and >0.9 Mann–Whitney U-test, Pearson uncorrected chi-square and Fisher exact test, respectively).

Mixed periapical status

Periapical status was either mixed or not stated in 10 studies; three randomized controlled trials (Pekruhn 1981, Mulhern *et al.* 1982, Albashaireh & Alnegrish 1998), five prospective cohort studies (O'Keefe 1976, Roane *et al.* 1983, Fava 1989, Walton & Fouad 1992, Imura & Zuolo 1995), one retrospective cohort study (Soltanoff 1978) and one cohort study in which the details were inadequate to determine whether it was prospective or retrospective (Oliet 1983). The studies in this category showed either no significant difference between the two (O'Keefe 1976, Soltanoff 1978, Pekruhn 1981, Mulhern *et al.* 1982, Oliet 1983, Fava 1989, Walton & Fouad 1992, Albashaireh & Alnegrish 1998) or significantly less postoperative pain/flare-up with a single-visit approach (Roane *et al.* 1983, Imura & Zuolo 1995).

Retreatment cases

Only one study was available in this category, which was a randomized controlled trial (Yoldas *et al.* 2004). Prevalence of flare-up was significantly higher with a single-visit approach (P-value = 0.05; Fisher exact test). The odds of flare-up occurring in single-visit root canal retreatment were 4.9 times that of multiple-visit treatment (odds ratio = 4.9; 95% CI: 1.1–19). The study showed a significant disadvantage of single-visit retreatment in terms of the frequency of flare-up. However, the P-value just reached a significant level (P-value = 0.05). Moreover, the 95% CI was rather wide, and the true odds ratio can be anywhere from 1.1 (merely no association between treatment approach and prevalence of flare-up) to 19 (the likelihood of single-visit retreatment having flare-up is 19 times of that of multiple-visit retreatment). The wide 95% CI indicates that more data should be collected before any definitive conclusions can be drawn about the strength of this association (Altman & Gardner 2000).

Data presentation

A graphical method was used to summarize results, giving a visual indication of the level of agreement amongst studies and a comprehensive qualitative view of the data (L'Abbé *et al.* 1987), hence the name 'L'Abbé plot' (Fig. 1). By plotting the event rate (prevalence of postoperative pain or flare-up in this analysis) in the treatment group (i.e. single-visit approach) on the vertical axis and that in the control group (i.e. multiple-visit approach) on the horizontal axis, a L'Abbé plot was constructed (Fig. 1). This plot

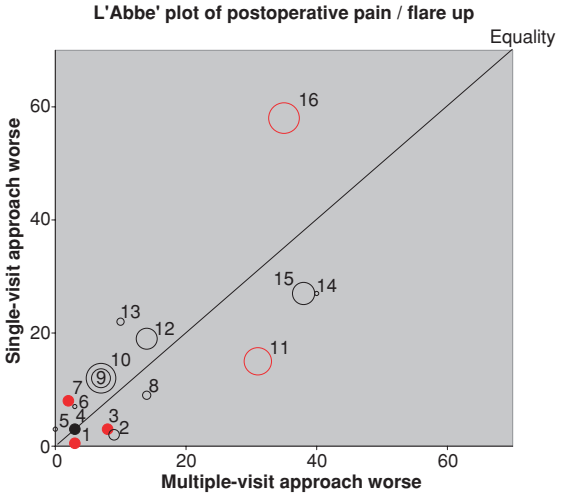

Figure 1 L'Abbé plot of 16 studies reporting prevalence of postoperative pain or flare-up in single- and multiple-visit root canal treatment. 1, Imura and Zuolo (1995); 2, O'Keefe (1976); 3, Eleazer and Eleazer (1998); 4, Walton and Fouad (1992); 5, Fava (1989); 6, Fava (1994); 7, Yoldas *et al.* (2004); 8, Al-Negrish and Habahbeh (2006); 9, Gesi *et al.* (2006); 10, Oliet (1983); 11, Roane *et al.* (1983); 12, Soltanoff (1978); 13, Pekruhn (1981); 14, Mulhern *et al.* (1982); 15, Albashaireh and Alnegrish (1998); 16, Ng *et al.* (2004). Unfilled circles are postoperative pain studies. Size of the circle is proportional to sample size of the group of 12 studies. Four filled circles are flare-up studies. Size of the circle is *not* proportional because their sample sizes are much larger than the rest of the studies. Red represents statistical significance, while black is not significant ($P > 0.05$).

helps readers think about the reasons why there is wide variation in results amongst included studies and about other factors that may influence the quality of studies.

Discussion

Heterogeneity of the studies

There are three potential sources of heterogeneity in clinical studies; clinical (variability in the participants and interventions), methodological (variability in trial design and quality) and statistical (variability in the treatment effects being evaluated in the different trials) (Deeks *et al.* 2005).

Pain is inherently subjective and pain measurement relies primarily on the verbal report of patients (Bromm 1984). The wide variation in the pain experience amongst individuals leads to a large variability in the pain scale ratings of patients who experience similar interventions. Specifically in the included studies, there were differences in the definition of each pain scale used. This means that even though different studies used the same four-point pain scales, each scale may have carried a different meaning and so did the degree of pain. In addition, the dichotomising point was different from one study to another. For example, in studies using a four-point pain scale, all of the following dichotomising cut off points were used: i.e. 1 vs. 2,3,4 or 1,2 vs. 3,4 or 1,2,3 vs. 4. These different dichotomising points made direct comparison amongst studies or statistical combination impossible. Furthermore, pain scale measurements are often interpreted in different ways by different researchers and clinicians, depending on the criteria they choose to apply (Farrar *et al.* 2000). Figure 1 clearly reflects this point, showing that the prevalence of postoperative pain varied considerably amongst studies (3–58%). As a result the data did not lend themselves to statistical manipulation such as meta-analysis, which statistically combines data from different studies and gives an overall quantitative meaning to the evidence. Not only was statistical or outcome heterogeneity large, methodological and clinical heterogeneity amongst the included studies was also far too great to conduct a meta-analysis and yield meaningful results (Deeks *et al.* 2005).

Study design

Level of evidence is ranked according to power to infer causality between studied factors (e.g. number of visits) and events (e.g. postoperative pain). The study design with greatest power is the randomized-controlled trial because it can minimize confounders, which are 'hidden' variables in a study that affect the events but are not known or acknowledged, and thus (potentially) distort the resulting data (McNamee 2003). This design can also maximize control over the environment, providing the most convincing causal relationship. The next best study design is the prospective cohort. This design lacks the randomization element but its prospective nature allows researchers to have more control over the environment compared with retrospective cohort studies. However, the best evidence does not depend solely on study design.

Clinical research reports that identify studies as randomized controlled trials require documentation of the randomization process (e.g. randomization-sequence generation, allocation assignment and implementation). These details were lacking in three of the

six studies (Pekruhn 1981, Mulhern *et al.* 1982, Yoldas *et al.* 2004) reported to be randomized controlled trials.

The clinical significance of postoperative pain and flare-up studies

Data from postoperative pain studies are often difficult to interpret because the clinical importance of the result is not obvious. The persistence of preoperative pain postoperatively may be a sign of an improving condition if the severity is reduced. The occurrence of minor transient postoperative pain will have little impact on the patients' well-being and is easily managed with medication. Determination of the proportion of patients who have clinically important pain (e.g. flare-up requiring emergency intervention) would provide a more interpretable result with direct clinical implications (Farrar *et al.* 2000). This will provide the clinician with information about the likelihood of a good or bad patient response. However, flare-up is rare (averaging 3% in three studies, i.e. Eleazer & Eleazer 1998, Imura & Zuolo 1995 and Walton & Fouad 1992); its clinical significance as a differentiating factor between single- versus multiple-visit treatment is therefore questionable. Thus, although flare-up is a good outcome measure because it is more clinically relevant and more clearly defined, it lacks clinical impact because of its low prevalence.

Future directions

Preoperative pain has been established as a major determinant (prognostic factor) of postoperative pain or flare-up (Torabinejad *et al.* 1988, Walton & Fouad 1992, Mattscheck *et al.* 2001). This should be recorded in future studies and the outcome measure should be reported in relation to improvement or deterioration rather than mere prevalence of postoperative pain/flare-up or a stand alone numerical value of a visual analogue pain scale (Farrar *et al.* 2000).

Any reports of future clinical studies should comply with CONSORT guideline against which important information (e.g. randomization process, masking procedures and justification of sample size) is checked before publication (Altman 1996, Altman *et al.* 2001). Sample size selection should be justified and reported. In essence, a study of small sample size (e.g. 30 per group) implicitly accepts that 3% prevalence of flare-up is not clinically different from 33% ($P = 0.05$, 90% power; reversed power and sample size calculation) because differences in prevalence of flare-up smaller than 30% will not reach statistical significance (Sokal & Rohlf 1995). Sample size selection and power of a study are fundamental and should be addressed at the design stage of any clinical study.

However, despite the shortcomings amongst the 16 studies to date, the value of conducting further studies must be questioned. The occurrence of minor, transient pain is not likely to be a determining factor in treatment choices, and the frequency of flare-ups has been documented to be low with both types of treatment.

Conclusion

Compelling evidence indicating a significantly different prevalence of postoperative pain/flare-up of either single- or multiple-visit root canal treatment is lacking. The low level of agreement amongst studies reflects the widely varying measures of pain severity, differences in treatment protocols and patient selection, as well as variability in treatment effects.

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