Effectiveness and Efficiency: Systematic Reflections on Single- and Multiple-visit Root Canal Treatment

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ABSTRACT

Single-visit root canal treatment was first documented in 1887. The controversy and debate within the dental community has been ongoing for over a century without resolution. The concept of evidence-based health practice has provided a structure on which the clinically-relevant questions in this debate can be dealt with systematically. When clinicians are faced with choices of which treatment regimen should be offered to patients, the central issues that should be considered are effectiveness, complications, patient/operator preference/satisfaction, and cost. Systematic review and meta-analysis techniques were used to reach definitive conclusions where high quality primary studies are available. The issue of satisfaction was studied using a quality of life concept, while the issue of cost was addressed by an economic evaluation (cost-minimization analysis). Treatment effectiveness and complications of single- and multiple-visit approach were similar. Patients overwhelmingly preferred single- over multiple-visit treatment with high satisfaction scores for both regimens. Australian endodontists were reluctant to embrace single-visit root canal treatment. Single-visit root canal treatment costs society less than multiple-visit treatment. On balance single-visit treatment offers substantial advantages with no identified adverse effects.
DECLARATION

This is to certify that the thesis comprises only my original work toward the PhD except where indicated in the preface; due acknowledgement has been made in the text to all other material used; the thesis is less than 100,000 words in length, exclusive of tables, maps, bibliographies and appendices.

Dr Chankhrit Sathorn
This thesis is based on the following publications.


This thesis consists of nine chapters; the first chapter is the introduction, statement of the problem and structure of the thesis. The second to the fifth chapters report the clinical findings, *i.e.* treatment effectiveness, complications, patient perceptions and cost. These chapters are in the form of manuscripts for publication as are chapters 6 to 8. The endodontists’ point of view is presented in chapter 6. Chapters 7 and 8 deal with the conflict in decision-making philosophy and potential explanations of the clinical results. The general discussion and future research directions are presented in chapter 9.

There is a certain degree of repetitiveness throughout the thesis especially in the introduction of each chapter, because each chapter is designed to be a stand-alone publication. Spelling and referencing formats differ in each chapter according to the requirements of the journal in which the manuscript has been (or is expected to be) published. References are included at the end of each chapter because of the structure of the thesis.
ACKNOWLEDGEMENT

This intellectual journey would never have been possible without support from a number of people.

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1 INTRODUCTION

This thesis grew out of a puzzle: why the debate on single- and multiple-visit root canal treatment has been going on for a century without resolution. Is there still a lack of reliable data even after 100 years? Why have we been unable to draw a conclusion? The attempt to complete root canal treatment in one visit has been documented since before the beginning of the twentieth century (Dodge 1887), although it was based on what is feasible rather than on biological considerations. Indeed, Miller's classic study of microorganisms in root canals had not yet been published (Miller 1894). The contemporary question, “Is single-visit root canal treatment a biologically compromised treatment?” has not been conclusively answered, although numerous studies have addressed various aspects of this question.

When clinicians are faced with choices of which treatment regimen should be offered to patients, the central issues that should be considered and compared are which regimen is more effective, easier to perform, less expensive, and has fewer adverse effects (Sackett 2000), and probably which regimen gives higher patient and operator satisfaction. In other words, the treatment of choice should be the most effective and the most efficient one with minimal risk of adverse consequences. Not only should the treatment of choice cure the disease more effectively and produce fewer complications, but it should involve less time, effort and cost. Single- vs. multiple-visit root canal treatment is a choice that clinicians face in daily practice.
THE EVIDENCE-BASED APPROACH

Recently, there has been a growing international interest in the development of measures to help ensure that practice decision making is better informed by the results of relevant and reliable research (Sutton 2000). Evidence-based health care is an integration of best available research evidence with clinical expertise and patient values (Sackett 2000). When these three elements are combined, clinicians and patients form a diagnostic and therapeutic alliance which optimises clinical outcomes and quality of life. Clinicians are faced with difficult questions and complex decisions every day; evidence-based health care provides scientifically solid foundations on which their decision making process can rely. Evidence-based concepts suggest that these foundations are: 1) research evidence, 2) clinical expertise (e.g. operator capability and satisfaction) and 3) patient values (e.g. patient satisfaction, cost) (Dawes 2005). Clinicians are continually overwhelmed with an unmanageable amount of health care information from a variety of sources. In dentistry alone, there are over 500 journals publishing over 43,000 research articles a year (Glenny et al. 2003). How do clinicians cope with this amount of information and yet still provide the current best available treatment to their patients? Evidence-based dentistry (EBD) can help by improving the decision-making process, making it more objective, consistent, and up-to-date. This ultimately improves the quality of treatment the clinician can provide and the level of healthcare for the patient. Evidence-based concepts use several techniques to achieve these goals, but the two most important tools of the trade are systematic reviews and meta-analyses.
**Systematic reviews and meta-analysis**

A systematic review is an evaluation and interpretation of all available research evidence relevant to a particular question. A concerted attempt is made to identify all relevant primary research, a standardized appraisal of study quality is made and the studies of acceptable quality are systematically and quantitatively synthesized (Glasziou 2001). A meta-analysis is a statistical methodology in which data from individual studies are considered and analyzed together (Upton & Cook 2002); by combining data they improve the ability to study the consistency of results, i.e. they could increase the statistical power. Without good quality primary data, however, meta-analyses are not particularly useful. The studies that potentially provide good quality primary data for secondary analysis (meta-analysis) are clinical studies such as randomized controlled clinical trials.

**Randomized controlled clinical trials**

Randomized controlled clinical trials (RCTs) are generally considered the most reliable method for assessing the efficacy of treatments (Elwood 1998), because they can minimize confounders and maximize control over the trial environment. RCTs are high in the hierarchy of quality of evidence (Greenhalgh 2006) because they can establish the most convincing causal relationship compared to other types of clinical studies, e.g. cohort, case control, and cross sectional survey. However, individual RCTs are often small and lack statistical power, owing mainly to their high cost and high degree of long-term commitment required. These shortcomings can be alleviated by the meta-
analysis technique, which can statistically combine the results from various studies and make the most out of currently available information.

**Evidence-based practice**

There are five steps involved in practising evidence-based concepts (Sackett 2000, Dawes 2005):

1. Converting the need for information (about prevention, diagnosis, prognosis, therapy, causation, etc) into an answerable question (PICO question: Problem, Intervention, Comparison, and Outcome).

2. Tracking down the best evidence with which to answer that question,

3. Critically appraising that evidence for its validity (closeness to the truth), impact (size of the effect), and applicability (usefulness in our clinical practice),

4. Integrating the critical appraisal with our clinical expertise and with our patient’s unique biology, values and circumstances.

5. Evaluating our effectiveness and efficiency in executing steps 1-4 and seeking ways to improve these for the next time.

To ensure sound clinical judgment, information is needed covering all aspects of single- and multiple-visit root canal treatment. This study was planned to compare comprehensively all relevant aspects of single- and multiple-visit root canal treatment.
THE BACKGROUND OF THE PROBLEM

It has been established beyond doubt that apical periodontitis is caused by bacteria within root canals (Kakehashi et al. 1965, Sundqvist 1976, Möller et al. 1981). Logically then, the management of apical periodontitis involves removal of the cause, i.e. bacterial eradication. Mechanical debridement combined with antibacterial irrigation (0.5% sodium hypochlorite) can render only 40-60% of the treated teeth bacteria-negative (Byström & Sundqvist 1983, Sjögren et al. 1997). Thus, the use of an antibacterial inter-appointment medicament has been advocated. Based on earlier data, dressing the canal for one week with calcium hydroxide was shown, in an evidence-based analysis, to increase the percentage of bacteria-free teeth (as measured by culturing canals) (Law & Messer 2004). By extrapolation, a multi-visit regimen including calcium hydroxide dressing between appointments has been considered mandatory to achieve a higher healing rate, because bacteria are further reduced (Spångberg 2001, Nair et al. 2005).

Despite this biological rationale in favour of multiple-visit treatment, single-visit root canal treatment has become common practice. It is believed to offer several advantages such as a reduced flare-up rate, good patient acceptance, and practice management considerations (Wahl 1996, Weine & Buchanan 1997). One survey study reported that almost 70% of US endodontists would treat teeth with a necrotic pulp and chronic apical abscess in one visit (Whitten et al. 1996). Another survey showed that around 70% of undergraduate teaching institutions in the USA encourage single-visit root canal treatment (Qualtrough et al. 1999). However, the fact that various practices are widely adopted does
not indicate that the practices are biologically sound. The argument for single visit treatment relies heavily on convenience, reduced post-operative pain and anecdotal patient acceptance. On the other hand, bacterial eradication cannot be predictably maximized without calcium hydroxide dressing between appointments; thus, the potential for healing may be compromised (Spångberg 2001, Nair et al. 2005). The issue is very controversial, and opinions vary greatly as to the relative risks and benefits of single- vs. multiple-visit root canal treatment.

**Points of comparison of alternative treatment regimens**

A comparison of effectiveness is usually the first point to be considered in clinical decision making. The direct evidence comparing healing rates following single- and multiple-visit root canal treatment should provide the answer as to which regimen is more effective. Several such studies have been conducted (Trope et al. 1999, Weiger et al. 2000, Peters & Wesselink 2002), but the number of included cases has generally been small because of the long-term nature of periapical healing.

Alternatively, a surrogate endpoint for treatment outcomes may be used, when the time and effort make a large, long-term clinical study impractical (De Gruttola et al. 2001). Surrogate endpoints are biomarkers representing a bridge between a mechanistic understanding of preclinical development and empirical clinical evaluation (Prentice 1989). The microbiological culture status of canals after medication is, in a way, a surrogate endpoint, which is used to predict clinical outcomes, i.e. healing of apical periodontitis. Although this surrogate
endpoint has been shown in one small clinical study to be significantly associated with a higher healing rate (Sjögren et al. 1997), the strength of this association has never been well quantified. The strength of this association might be the determining factor in the clinical significance of calcium hydroxide medication. Ultimately, however, healing (true endpoint) remains the ideal measure of the effectiveness of the two treatment regimens (Fleming & DeMets 1996).

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. Prevalence of postoperative pain or flare-up (adverse effects) is, therefore, one of the influencing factors when making a clinical decision.

Outcome measures have evolved from simple binary variables such as survival or occurrence of clinical events (e.g. healing of apical periodontitis) to complex patient-oriented measures, ranging from functional disability scales to quality of life. The introduction of the patients’ point-of-view in quality and effectiveness studies can be considered a further step towards a more comprehensive humanistic approach to the patient, who is seen as a ‘complex individual’ member of a dynamic community and not a ‘complex machine’ assembled with separate organ systems (Apolone & Mosconi 1998). It has been widely accepted that patients should be involved in treatment decision making. By capturing the degree of discomfort that patients experienced during or after the treatment,
and also overall patient satisfaction with the treatment, a systematic comparison of treatment regimens is possible. Based on this information, patients would have their say in treatment decision making.

The question of cost is increasingly playing a role in health care decisions. With a limited pool of money available through the publicly-funded health care system, decisions have to be made about which treatments should be funded and which should not. In the private sector, on the other hand, where direct public funds are less involved, cost considerations can still be far beyond out-of-pocket treatment fee e.g. patient anxiety, discomfort, time and traveling expenses. Almost every health care intervention has an impact not only on health and social welfare but also on the resources used in the production of health care services. Resources have alternative beneficial uses and different people may place different values on the various health outcomes. Thus, to make the best decisions about alternative courses of action, information is needed on the health benefits and also the extent of resource use (or opportunity cost) of these courses of action (Donaldson et al. 2002). Economic evaluation is, therefore, needed to inform clinicians and also policymakers.

A comprehensive comparison of two alternative treatment regimens has never been performed in endodontics. This study was undertaken to provide such a comparison, and to assist clinicians in making informed treatment decisions based on the current best available scientific evidence.
OBJECTIVES OF THE STUDY

Single- and multiple-visit root canal treatment are two competing alternative forms of treatment. Multiple-visit treatment requires several shorter appointments, generally with an inter-appointment intracanal medication, while single-visit is the completion of root canal treatment in one longer appointment.

The aims of this study were to compare six aspects of the two alternative treatment regimens, namely;

1. Treatment outcomes: differences in healing frequency of apical periodontitis.

2. Adverse effects: differences in the prevalence of postoperative pain and flare up.

3. Patient perceptions: treatment regimen preference of patients.

4. Cost: difference in net cost of the two regimens.

5. Endodontist perceptions: treatment regimen preference, factors influencing treatment decision and adoption of change.


6.1. A critical appraisal of the significance of microbiological root canal sampling (positive and negative cultures) in predicting treatment outcome.
THE STRUCTURE OF THE THESIS

The study consisted of six independent parts according to the study objectives as outlined above.

Treatment outcomes and adverse effects

These issues have been addressed by a number of previous studies, so that a systematic review technique was chosen to establish the current state of knowledge.

Patient perceptions

Human beings act and behave differently and sometimes irrationally. In cancer therapy, patients might prefer a less effective treatment regimen (lower 5 year survival rates), if the regimen provided a comparatively higher quality of life (Lloyd et al. 2008). This viewpoint might not make sense to clinicians who hold the view that life extension is the only aim of health care, but that is why a study of the patient’s point of view is important in clinical practice (Kaplan 1999).

A quality of life (QoL) instrument was constructed based largely on two articles studying patient quality of life in oral surgery and endodontics (Shugars et al. 1996, Dugas et al. 2002). The assumption was made that a single-visit root canal treatment would need a longer visit to finish than each multiple-visit appointment. Attributes were designed to detect discomfort as a result of long treatment. Overall discomfort and treatment satisfaction were assessed for 92 patients using a modified visual analogue pain scale (Miller & Ferris 1993).
Introduction

Cost
The societal perspective analysis was adopted adhering to a reference case scenario- a set of standardized practices for conducting an economic evaluation (Gold 1996). The analysis considers everyone affected by the intervention and counts all significant health outcomes and costs that flow from it, regardless of who experiences the outcomes or costs, i.e. all costs are included in the study. The analysis was conducted on data collected during the treatment of the same 92 patients as in the previous section.

Endodontist perceptions
Endodontists’ perceptions of the two treatment regimens can be influential in treatment decision making. It must, therefore, be studied to complete the picture. Fifty two Australian endodontists (71% of all registered specialists in Australia) were interviewed and their perceptions, preferences, and objections were collected and analyzed.

Biological aspect
A number of good quality studies have investigated this issue, however, they have never been systematically identified nor combined quantitatively with proper statistical methods. Thus, antibacterial efficacy of calcium hydroxide was studied using a systematic review and meta-analysis.

Critical appraisal of microbiological root canal sampling
Intuitively, clinicians universally accept root canal culturing as a way of predicting endodontic treatment outcomes. The general accepted notion is that the more bacteria can be reduced, the higher the ‘potential’ healing rates will be.
In other words, root canal culturing is often considered as a surrogate endpoint for healing. A comprehensive search was performed to identify the evidence that links root canal culturing to clinical outcome (healing rates). The quality of this surrogate endpoint was determined using four measurements to test its accuracy (i.e., sensitivity, specificity, positive predictive value, and negative predictive value).
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2 CLINICAL FINDINGS: TREATMENT OUTCOMES

Effectiveness of single- versus multiple-visit endodontic treatment of teeth with apical periodontitis: a systematic review and meta-analysis.

A manuscript published in


RESEARCH QUESTION:
Is healing rate of single- or multiple-visit root canal treatment higher and to what extent?
ABSTRACT

Aim The clinical question this review aimed to answer is: Does single visit root canal treatment without calcium hydroxide dressing, compared to multiple visit treatment with calcium hydroxide dressing for one week or more, result in a lower healing (success) rate (as measured by clinical and radiographic interpretation)?

Methodology CENTRAL, MEDLINE, EMBASE, and HEALTH STAR databases were used. 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 studies were randomized controlled clinical trials (RCTs) comparing healing rate of single- and multiple-visit root canal treatment in humans. The outcome measured was healing of radiographically detectable lesions. Data in those studies were independently extracted.

Results Only three RCTs were identified and included in the review, covering 146 cases. Sample size of all three studies was small; none demonstrated a statistically significant difference in healing rates. Risk differences of included studies were combined using the inverse variance-weighted method ($RD_{Pooled} = -6.3\%;\ 95\%\ CI: \ -20.3\% \text{to} \ 7.8\%$).

Conclusion Based on the current best available evidence, single-visit root canal treatment appeared to be slightly more effective than multiple visit i.e.
6.3% higher healing rate. However, the difference in healing rate between these two treatment regimens was not statistically significant (p=0.3809).
INTRODUCTION

It has been established beyond doubt that apical periodontitis is caused by bacteria within root canals (Kakehashi et al. 1965, Möller et al. 1981). Logically, the treatment of apical periodontitis should be removal of the cause, i.e. bacterial eradication. Mechanical debridement combined with antibacterial irrigation (0.5% sodium hypochlorite) can render 40-60% of the treated teeth bacteria-negative (Byström & Sundqvist 1983, Sjögren et al. 1997). In addition to mechanical debridement and antibacterial irrigation, dressing the canal for one week with calcium hydroxide has been shown to increase the percentage of bacteria-negative teeth to around 70% (Law & Messer 2004). By extrapolation, the regimen including calcium hydroxide dressing between appointments should provide a higher healing rate, because bacteria are further reduced. Thus, the healing rate of multiple-visit treatment should be higher than single-visit treatment (without calcium hydroxide dressing).

Single-visit root canal treatment has become common practice and offers several advantages such as a reduced flare-up rate (Walton & Fouad 1992, Imura & Zuolo 1995, Albashaireh & Alnegrish 1998), good patient acceptance, and practice management considerations. One survey study reported that almost 70% of endodontists would treat teeth with a necrotic pulp and chronic apical abscess in one visit (Whitten et al. 1996). Another survey showed that around 70% of undergraduate teaching institutions in the USA encourage single-visit root canal treatment (Qualtrough et al. 1999). However, the fact that various practices are widely adopted does not indicate that the practices are
biologically sound and/or appropriate. The argument for single visit treatment relies heavily on convenience, patient acceptance and reduced post-operative pain. On the other hand, bacterial eradication cannot be predictably maximized without calcium hydroxide dressing between appointments; thus, the potential for healing may be compromised (Spångberg 2001). The issue is very controversial, and opinions vary greatly as to the relative risks and benefits of single- vs multiple-visit root canal treatment. The direct evidence comparing healing rates following single- and multiple-visit root canal treatment should provide insight as to which regimen is more effective.

Randomized controlled clinical trials (RCTs) are generally considered the most reliable method for assessing the efficacy of treatments (Elwood 1998), because they can minimize confounders and maximize control over the trial environment. RCTs are high in the hierarchy of quality of evidence (Greenhalgh 2006) because they can establish the most convincing causal relationship compared to other types of clinical studies, e.g. cohort, case control, and cross sectional survey. However, individual RCTs are often small and lack statistical power, owing mainly to their high cost and high degree of long-term commitment required. A meta-analysis is a statistical methodology in which data from individual RCTs are considered and analyzed together (Upton & Cook 2002); by combining data they improve the ability to study the consistency of results, i.e. they give increased power.

There has been a growing international interest in the development of measures to help ensure that practice decision making is better informed by the results of relevant and reliable research (evidence-based) (Sutton 2000). A systematic
review is one of those measures. It is an evaluation and interpretation of all available research evidence relevant to a particular question. A concerted attempt is made to identify all relevant primary research, a standardized appraisal of study quality is made and the studies of acceptable quality are systematically and quantitatively synthesized (Glasziou 2001).

This systematic review addresses the choices (single- or multiple-visit root canal treatment) clinicians face in dental practice, and aims to provide the current best available evidence upon which clinical decisions regarding root canal treatment can be based. The clinical question to be answered in this systematic review was framed in terms of a PICO question [problem (P), intervention (I), comparison (C), and outcome (O)] as follows: In patients undergoing root canal treatment for apical periodontitis (teeth with an infected root canal system), does single-visit treatment without calcium hydroxide dressing, compared to multiple-visit treatment with calcium hydroxide dressing for one week or more, result in a lower healing (success) rate (as measured by clinical and radiographic interpretation)?

**MATERIALS AND METHODS**

**Literature search**

Randomized controlled trials and controlled clinical trials of single- versus multiple-visit root canal treatment conducted in humans were identified. The Cochrane Controlled Trials Register (CENTRAL) was searched using the term ENDODONTICS, SINGLE, ONE, TWO, MULTIPLE, VISIT$, APPOINTMENT$. The optimum search strategy for detecting controlled trials formulated by the
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Cochrane Collaboration as outlined in the Cochrane Reviewers’ Handbook (Alderson et al. 2004) was combined with the above-mentioned terms and used to search MEDLINE from 1966 to August 2004 (Table 2.1). A similar search was undertaken on EMBASE (1988 to 2004) and HealthSTAR. No language restriction was applied to the search. One hundred and ninety six studies were subjected to the preliminary analysis. Two reviewers scanned all titles and abstracts (Edwards et al. 2002), where available, and decided whether or not they were related to healing rate of single- or multiple-visit root canal treatment. Where information from the title and abstract was not adequate in determining the paper’s relevance, they were automatically included in subsequent analysis. One hundred and seventy three studies were excluded from the list, and the 23 remaining articles were subjected to stricter exclusion criteria.

Inclusion and exclusion criteria

The full text articles of the remaining studies were then obtained and reviewed by the two reviewers, and the inclusion criteria (Table 2.2) were applied independently. Reference lists from identified articles were scanned to identify other potentially relevant articles (one more article was identified (Friedman et al. 1995)). 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 (www.isinet.com), to identify potentially relevant subsequent primary research (Glasziou 2001) (one more article was identified (Farzaneh et al. 2004)).
**Data extraction**

A systematic data extraction sheet constructed by The Critical Appraisal Skills Programme (CASP) (Learning and Development, Public Health Resource Unit NHS, UK) ([http://www.phru.nhs.uk/casp/casp.htm](http://www.phru.nhs.uk/casp/casp.htm) last accessed June 28, 2004) and CONSORT guidelines (Begg et al. 1996, Newcombe 2004) were adapted by the reviewers who independently extracted the data. Authors of two studies were contacted to acquire additional information not available in the published article.

**Meta-Analysis**

Between-study heterogeneity was assessed using standard \( \chi^2 \) test or Q statistic. The principal measure of treatment effect was risk difference, which is defined as the risk in the experimental group minus risk in the control group. For the purpose of this study it is given as the difference in healing rates between single- and multiple-visit treatment. Risk difference is a measure of the impact of the treatment on the number of events (healing), since it takes into account the prevalence of the event, i.e. how common it is. This is in contrast to odds ratio, which is a measure of the association between treatment and outcome, but does not give an indication of the impact of the intervention, i.e. the same odds ratio can give a different impact depending on how common the event is (Sutton 2000). The fixed effect method for combining study estimates was used and an overall estimate was produced. Risk differences of included studies were combined using the inverse variance-weighted method, by which each study was given a weight directly proportional to its precision (Sutton 2000).
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(Comprehensive Meta Analysis Version 1.0.25, Biostat, Englewood, NJ, USA).
The level of statistical significance is set at 0.05.

RESULTS

Included and excluded studies
Only three small randomized controlled clinical trials met our inclusion criteria (Table 2.2): that is, (Trope et al. 1999, Weiger et al. 2000), and (Peters & Wesselink 2002). Five studies (Soltanoff 1978, Rudner & Oliet 1981, Oliet 1983, Friedman et al. 1995, Farzaneh et al. 2004) that compared healing rate of single- and multiple-visit root canal treatment were excluded, mainly because their patient allocations were not randomized. Other studies were excluded because of different reasons as shown in Table 2.3.

Data summary of included studies
Randomization could well be the single most important design feature of a study investigating therapeutic efficacy because it is the only way to control for confounders that are not known or not measured (Alderson et al. 2004). Randomization was explicitly stated in Trope et al. (1999) and Peters et al. (2002), but not reported by Weiger et al. (2000). Randomization was, however, implicitly stated using the term ‘minimization’, which is one of several patient randomization systems. Overall, randomization was reasonably adequate in all three studies, even though it was not detailed and was not as stringent as required by CONSORT guidelines.
The differences between subjects of treatment groups at entry to the trial might act as a significant confounder. The differences in severity of apical periodontitis (high PAI score) might affect healing time and/or chance of healing. Trope et al. (1999) solved the problem of differences in severity of apical periodontitis by baseline adjustment, using a periapical index (PAI), and including only subjects with PAI score 3 or more. The periapical index (PAI) scoring system is a 5-point scale radiographic interpretation designed to determine the absence, presence, or transformation of a disease state as score 1 is healthy periapical tissue and score 5 is severe apical periodontitis with exacerbating features (Ørstavik et al. 1986). Healing was judged as a decrease in the PAI score overtime. Even though differences in subjects could be balanced, it also decreased their sample size (almost 50% reduction in the single visit group) and statistical power was decreased a great deal. Weiger et al. (2000) implemented a minimization technique to dynamically balance different tooth types between the two treatment groups. Peters et al. (2002) did not mention any attempts to balance differences between subjects of the two treatment groups.

Sample size ranged from 17 to 36 teeth per treatment group. None of the papers reported rationale for the sample size. Endodontic treatment performed in all studies seemed to be standard. Sodium hypochlorite was used as an irrigant with concentration 1-2.5%. However, effects of different NaOCl concentrations on outcomes have not been demonstrated. Calcium hydroxide was used with different duration (1-4 wks). Again, duration of calcium hydroxide dressing
seems to be inconsequential once a 1-week duration is reached (Sjögren et al. 1991).

**Assessment of healing**

One-year follow up time is the soonest possible to determine whether or not the lesion has healed (Ørstavik 1996). Follow up time in all three studies was adequate, with patients followed for 1-5 years. The follow up period in some instances, however, is less than ideal since many cases do not show complete healing for 4-5 years. In the study of Weiger et al. (2000), cases were mostly followed until complete healing occurred regardless of time interval (6 months – 5 years) Trope et al. (1999) used one year as a cut off point, which might appear to be a shortcoming in cases where the lesion had not completely healed. However, this study utilized a different scoring system (PAI score) (Ørstavik et al. 1986), and the teeth with a decreased PAI score were deemed healed, even though they might not have normal PDL width.

Internal validity or observation consistency is an extremely important issue in randomized controlled trials; without it, systematic bias is ensured. Radiographic interpretation is very subject to human visual perception. Trope et al. (1999) was the only paper exercising an extensive calibration of evaluators. Calibration was implicitly stated in Peters et al. (2002) by brief mentioning of kappa score. Blinding is another technique to minimize systematic bias; all three studies clearly stated, though without specific details, the use of blinding.

A low recall rate affects study credibility a great deal because lost samples are not accounted for and their treatment results cannot be obtained. This does not
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seem to apply here, as all three studies presented a very high recall rate (92-100%).

**Meta-Analysis**

Outcomes of individual studies and a summary of meta-analysis results are shown in Table 2.4, Table 2.5 and Figure 2.1. No studies demonstrated a statistically significant difference in healing rate (therapeutic efficacy) between single- and multiple-visit treatment. Meta-analysis was performed on the combined data. The outcome measure (healing rate) was based on binary data i.e. healed/not-healed. A comparison was made between single- and multiple-visit groups, thus outcome measures were comparative binary outcomes (Sutton 2000). Between-study heterogeneity was assessed using the standard $\chi^2$ test or Q statistic. The three studies were homogeneous (Test of Homogeneity Cochran Q (ChiSq)=1.724 df=2 p=0.4222). A graphical informal test (Forest plot) also confirmed the homogeneity (Figure 2.1). Thus, fixed effect methods for combining study estimates were used and overall estimate was produced. Risk differences of included studies were combined using the inverse variance-weighted method ($RD_{\text{pooled}} = -6.3\%; \text{95\% CI:} -20.3\%\text{to} 7.8\%)$. Based on the current best available evidence, single-visit root canal treatment appeared to be slightly more effective than multiple-visit, i.e. a 6.3% higher healing rate. However, the difference in healing rate between the two treatment regimens was not statistically significant (p=0.3809)

**DISCUSSION**

*Three small studies are not strong evidence for making clinical decisions.*
A wide confidence interval (28.1%) of pooled risk difference indicated low statistical power or low precision, in other words, the impact of single-visit treatment was weak on providing better treatment outcomes. Even though the 95% confidence interval of pooled risk difference was wide, it was narrower than individual studies indicating a higher precision (Figure 2.1).

Publication bias (the tendency that positive studies are more likely to be published than negative ones) cannot be ruled out. However, a publication bias test (e.g. the funnel plot) was not performed because it would be unrealistic to perform such a test accurately on the very small number of RCTs. Another potential source of bias is differences in characteristics of subjects between the single- and multiple-visit groups. In clinical studies, these differences always exist, but imbalances in factors that are not prognostic cannot fairly be considered sources of bias (Burton et al. 2004). In root canal treatment, there is only one consensual preoperative prognostic factor, that is, a radiographically detectable lesion or the presence of apical periodontitis. This potential bias did not apply here because a radiographically detectable lesion was present in all subjects as part of the inclusion criteria. Other potential prognostic factors, e.g. lesion size, pulpal status, symptoms and tooth type have never been proven. The impact of those factors is contradictory or inconclusive at most (Friedman 1998). Operators in all three studies were experienced endodontists; thus extrapolation of the results of this review to general practitioners may not be entirely appropriate. A large number of cross-sectional studies indicated that technical quality of root canal treatment in many countries is frequently low (Dugas et al. 2003). The focus of root canal treatment should be on the highest
possible technical standard with good bacterial control rather than completing
treatment in the shortest number of appointments.

Sample size in all three studies was unjustifiably but understandably small.
This demonstrates an important limitation of RCTs in dentistry. The proper
sample size should be calculated prior to trial. The sample size (power
statistics) depends on the healing rate difference that is considered clinically
significant. The higher the difference, the smaller the sample size. The highest
possible healing rate difference could be taken from the study of Sjögren et al.
(1997), that is 26% (94% vs 68% healing rates in negative and positive cultured
teeth, respectively). The sample size required for this difference at p=0.05 and
80% power is 64 in total (32/group.) (Sokal & Rohlf 1995), which is the smallest
sample size possible. On the other hand, the Toronto study (Farzaneh et al.
2004) judged differences between outcomes of less than 10% to be trivial; if we
were to conduct the trial anticipating a 10% difference, the upper limit of the
sample size should then be 430 in total (90% vs 80% expected healing rate) or
622 in total (80% vs 70% expected healing rate) at p=0.05, 80% power. It took
two endodontists 5 years to recruit 67 patients in one of the included studies
(Weiger et al. 2000), so that, an individual study that can detect the small
difference (10%) in healing rate of single- and multiple-visit endodontics is
never likely to become available.

When a study shows no statistically significant difference between treatment
modalities (p>0.05), either there is genuinely no difference between the
treatments or there were too few subjects to demonstrate such a difference if it
existed. It does not tell us which. The meta-analysis showed no statistically
significant difference (p=0.381) in healing rate of the two treatment regimens. The upper 95% confidence interval of the pooled risk difference was 7.8% in favour of multiple-visit (Table 2.5), indicating that if a larger trial was conducted, there would be only a 2.5% chance that a difference larger than 7.8% would be found. As less than 10% difference is considered to be clinically unimportant (Farzaneh et al. 2004), it is highly unlikely that a larger trial would find a larger, significant difference in favour of multiple-visit root canal treatment. The non-significant result demonstrated here could thus be considered definitive in the sense that single-visit treatment is not likely to lead to a lower healing rate than multiple-visit treatment (<10% healing rate differential), although it must be acknowledged that the level of evidence is weak.

Of the additional studies that were excluded due to lack of randomization, similar differences of 10% or less were also found (Soltanoff 1978, Rudner & Oliet 1981, Oliet 1983, Friedman et al. 1995, Farzaneh et al. 2004).

*The biological argument is not supported by clinical evidence.*

The biological benefit of multiple-visit treatment is that bacterial load can be further reduced by an antibacterial dressing between appointments. Based on clinical outcomes, no additional benefit is provided by the use of an inter-appointment antibacterial dressing such as calcium hydroxide. Probably, elimination of bacteria is not strictly necessary, and maximum reduction of bacteria and effective canal filling may be sufficient in terms of healing, rather than complete eradication.
In a study that examined the influence of infection at the time of root filling on the outcome of treatment (Sjögren et al. 1997), 68% of teeth which were infected at the time of root filling, healed after the treatment. Similar results have also been reported in other studies (Sundqvist et al. 1998, Katebzadeh et al. 2000). While infection at the time of root filling will adversely affect the outcome of treatment, the presence of a pathogen, alone, is not sufficient for persistence of disease. There must be other factors that occur in combination to result in persistence of endodontic disease (Sundqvist & Figdor 2003), and calcium hydroxide dressing might not be able to affect these factors.

**Clinical recommendations based on results**

When clinicians are faced with choices of which treatment regimen should be offered to patients, the central issues that should be considered are which regimen does more good than harm, which regimens are worth the effort, and the cost of using them (Sackett 2000), and probably which regimen gives higher patient and operator satisfaction. This review addressed only the first question (treatment effectiveness). The other three questions still remain open for further research.

In terms of therapeutic efficacy, current best available evidence failed to demonstrate a difference between the two treatment regimens. The worst-case scenario of healing rate of single-visit endodontics was 7.8% (upper 95% CI, Table 2.5) less than with multiple-visit treatment. In view of public health policy decisions, this can be considered insignificant, especially when contrasted with the lower end of 95% CI (20.3% higher healing rate in favour of single visit, Table 2.5). On the other hand, as clinicians dealing with individual patients, we
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will strive for the best possible bacterial control, in an effort to maximize prospects for healing.
ADDENDUM

Since the publication of this study in 2005, there have been two more randomized-controlled clinical trials (Molander et al. 2007, Penesis et al. 2008) and one high quality prospective cohort study (de Chevigny et al. 2008) published, none of which showed a significant difference in healing rates between single- and multiple-visit root canal treatment. While specific details of treatment differed among studies (Molander et al. 2007 used an IKI rinse in the single visit group, Penesis et al. 2008 placed a Ca(OH)$_2$ / Chlorhexidene mix as intracanal medicament), outcomes were similar. Also, two systematic reviews (Figini et al. 2007, Ng et al. 2008) drew the same conclusion.

Hence, despite criticism (please see Appendix IV for details), no evidence has emerged in the past three years since this systematic review was published, that multi-visit treatment achieves a better outcome.
Table 2.1 MEDLINE (Ovid) search strategy developed to find articles related single visit endodontics

<table>
<thead>
<tr>
<th>Search History</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Endodontics/ or apicectomy/ or dental implantation, endosseous, endodontic/ or dental pulp capping/ or pulpectomy/ or pulpotomy/ or “root canal therapy”/ or dental pulp devitalization/ or “root canal obturation”/ or retrograde obturation/ or “root canal preparation”/ or tooth replantation/</td>
<td>16064</td>
</tr>
<tr>
<td>2 One .mp. [mp=title, original title, abstract, name of substance, mesh subject heading]</td>
<td>1349112</td>
</tr>
<tr>
<td>3 Single.mp. [mp=title, original title, abstract, name of substance, mesh subject heading]</td>
<td>523388</td>
</tr>
<tr>
<td>4 Two.mp. [mp=title, original title, abstract, name of substance, mesh subject heading]</td>
<td>1771618</td>
</tr>
<tr>
<td>5 Multiple.mp. [mp=title, original title, abstract, name of substance, mesh subject heading]</td>
<td>336124</td>
</tr>
<tr>
<td>6 Visit$.mp. [mp=title, original title, abstract, name of substance, mesh subject heading]</td>
<td>51432</td>
</tr>
<tr>
<td>7 Appointment$.mp [mp=title, original title, abstract, name of substance, mesh subject heading]</td>
<td>8983</td>
</tr>
<tr>
<td>8 2 or 3 or 4 or 5</td>
<td>3050842</td>
</tr>
<tr>
<td>9 6 or 7</td>
<td>59289</td>
</tr>
<tr>
<td>10 1 and 8 and 9</td>
<td>210</td>
</tr>
<tr>
<td>11 Limit 10 to human</td>
<td>196</td>
</tr>
</tbody>
</table>
### Table 2.2 Inclusion and exclusion criteria used in the analysis

<table>
<thead>
<tr>
<th>Inclusion criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Subjects had a non-contributory medical history;</td>
</tr>
<tr>
<td>2. Subjects presented with mature teeth with infected necrotic root canals and</td>
</tr>
<tr>
<td>radiographic evidence of periapical bone loss (as an indication of pre-operative</td>
</tr>
<tr>
<td>canal infection);</td>
</tr>
<tr>
<td>3. All selected root canals had not received any endodontic treatment previously;</td>
</tr>
<tr>
<td>4. Subjects underwent non-surgical root canal treatment during the study;</td>
</tr>
<tr>
<td>5. The outcome measure was the number of teeth that showed radiographic evidence of</td>
</tr>
<tr>
<td>healing.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Exclusion criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Inclusion of test teeth without infected necrotic root canal systems and/or</td>
</tr>
<tr>
<td>radiographic evidence of periapical bone loss (hence no preoperative canal infection);</td>
</tr>
<tr>
<td>2. Subjects were not randomly assigned to single- or multiple-visit treatment;</td>
</tr>
<tr>
<td>3. Study carried out on failed, endodontically treated teeth (retreatment cases);</td>
</tr>
<tr>
<td>4. No comparison between single- and multiple-visit endodontics within the same study;</td>
</tr>
<tr>
<td>5. No healing rate presented.</td>
</tr>
</tbody>
</table>
Table 2.3 Studies excluded from and included in the systematic review

<table>
<thead>
<tr>
<th>Excluded studies</th>
<th>Exclusion criteria</th>
<th>Included studies</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Wolch 1975)</td>
<td>5</td>
<td>(Trope et al. 1999)</td>
</tr>
<tr>
<td>(Soltanoff 1978)</td>
<td>1, 2</td>
<td>(Weiger et al. 2000)</td>
</tr>
<tr>
<td>(Ashkenaz 1979)</td>
<td>4</td>
<td>(Peters &amp; Wesselink 2002)</td>
</tr>
<tr>
<td>(Fujita &amp; Nagasawa 1979)</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>(Pekruhn 1981)</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>(Rudner &amp; Oliet 1981)</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>(Lipton 1982)</td>
<td>Unable to locate,</td>
<td></td>
</tr>
<tr>
<td></td>
<td>after repeated</td>
<td></td>
</tr>
<tr>
<td></td>
<td>attempts</td>
<td></td>
</tr>
<tr>
<td>(Oliet 1983)</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>(Pekruhn 1986)</td>
<td>1, 2, 3, 4</td>
<td></td>
</tr>
<tr>
<td>(Petrovic et al. 1990)</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>(Yamada 1992)</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>(Jurcak et al. 1993)</td>
<td>1, 4</td>
<td></td>
</tr>
<tr>
<td>(Fava 1994)</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>(Friedman et al. 1995)</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>(Sjögren et al. 1997)</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>(Kenrick 2000)</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>(Soares &amp; Cesar 2001)</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>(Wolcott 2002)</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>(McFarland 2003)</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>(Field et al. 2004)</td>
<td>1, 2, 4</td>
<td></td>
</tr>
<tr>
<td>(Farzaneh et al. 2004)</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>(Kvist et al. 2004)</td>
<td>5</td>
<td></td>
</tr>
</tbody>
</table>
Table 2.4 Data summary of included studies

<table>
<thead>
<tr>
<th>Citation</th>
<th>N total</th>
<th>Observation time (yrs)</th>
<th>Number of teeth (not healed/total) in Single visit gr.</th>
<th>Number of teeth (not healed/total) in Multiple visit gr.</th>
<th>Healing rate (%)</th>
<th>Single vs Multiple visit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trope <em>et al.</em> 1999</td>
<td>41</td>
<td>1</td>
<td>8/22</td>
<td>5/19</td>
<td>64% vs 74%</td>
<td></td>
</tr>
<tr>
<td>Weiger <em>et al.</em> 2000</td>
<td>67</td>
<td>0.5-5</td>
<td>6/36</td>
<td>9/31</td>
<td>83% vs 71%</td>
<td></td>
</tr>
<tr>
<td>Peters &amp; Wesselink 2002</td>
<td>38</td>
<td>4.5</td>
<td>4/21</td>
<td>5/17</td>
<td>81% vs 71%</td>
<td></td>
</tr>
<tr>
<td>Combined 3 studies</td>
<td>146</td>
<td>N.A.</td>
<td>18/79</td>
<td>19/67</td>
<td>77% vs 71%</td>
<td></td>
</tr>
</tbody>
</table>
### Table 2.5 Meta-Analysis data summary (Minus value indicates the difference is in favour of single-visit endodontics.)

<table>
<thead>
<tr>
<th>Citation</th>
<th>Risk difference (%)</th>
<th>95%CI (%)</th>
<th>Weight (%)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Lower</td>
<td>Upper</td>
<td></td>
</tr>
<tr>
<td>Trope et al. 1999</td>
<td>10.0</td>
<td>-18.2</td>
<td>38.3</td>
<td>48.25 (24.8)</td>
</tr>
<tr>
<td>Weiger et al. 2000</td>
<td>-12.4</td>
<td>-32.5</td>
<td>7.7</td>
<td>95.20 (49)</td>
</tr>
<tr>
<td>Peters &amp; Wesselin 2002</td>
<td>-10.4</td>
<td>-37.8</td>
<td>17</td>
<td>51.14 (26.2)</td>
</tr>
<tr>
<td>Combined 3 studies</td>
<td>-6.3</td>
<td>-20.3</td>
<td>7.8</td>
<td>N.A.</td>
</tr>
</tbody>
</table>
Figure 2.1 Forest plot

Horizontal line in Forest plot shows the 95% confidence interval; the shorter the line, the higher the precision of the study.

Negative and positive value of risk difference is used to indicate the differences in direction of the value.

Black boxes indicate the mean risk difference; their sizes are proportional to their sample size.

The transparent diamond is the pooled result, with horizontal tips indicating 95% confidence interval, and the vertical tips indicating pooled risk difference.

The vertical line at 0% indicates no healing rate difference between the two treatment regimens.
REFERENCES:


Clinical outcomes


3 CLINICAL FINDINGS: ADVERSE EFFECTS

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

A manuscript published in


RESEARCH QUESTIONS:

Is postoperative pain/flare-up rate higher for single- or for multiple-visit root canal treatment?

Are there adverse consequences of single-visit root canal treatment?
ABSTRACT

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 among included studies was far too great to conduct a 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.
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 before the beginning of the twentieth century (Dodge 1887), yet we have not come to a definitive conclusion. Some of the unresolved issues include differences in clinical outcomes, microbiological concerns, 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 regimen 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 a necrotic pulp and apical periodontitis (Sathorn et al. 2005). Complications of these two treatment approaches, though, have not yet been studied systematically.

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 regimen 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 believed 25 years ago 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:

1) In patients undergoing endodontic 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 endodontic 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, while 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 to require 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/](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 3.1). 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 to 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. Two hundred and seventeen 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. Two hundred studies were excluded from the list, and the twenty remaining articles were subjected to stricter exclusion criteria.

**Inclusion and exclusion criteria**

The full texts of the remaining papers were then obtained and reviewed, and the inclusion criteria (Table 3.2) 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 3.3). 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.

RESULTS

Data summary of included studies

Sixteen studies were included in the analysis (Table 3.4). 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). Among 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 among studies in type of instrumentation technique, medication, and concentration of sodium hypochlorite used as the irrigant. Overall, the clinical procedures followed currently accepted standards, with the following variations: 1) Albashaireh &
Adverse effects

Alnegrish (1998), Imura & Suolo (1995), Mulhern et al. (1982) and Walton & Fouad (1992) left canals empty between appointments; 2) Eleazer & Eleazer (1998), Fava (1989), and Pekruhn (1981) used metacresylacetate, CMCP and formocresol as intracanal medication respectively; 3) 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 0.5-5.25%. 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 Alnegrish & 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 three flare-up studies. The remaining studies used four, five or 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 hours to 30 days, with different recording frequency. Most studies reported measurement at 48 hours. 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- vs multiple-visit treatment (such as healing).

a) 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 to 4.7). Eleazer & Eleazer (1998) reported opposite results using flare-up rate as the 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 to 7.1).

b) 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
Adverse effects

(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).

c) Mixed periapical status


d) 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 to 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 among studies and a comprehensive qualitative view of the data (L’Abbé et al. 1987), hence the name “L’Abbé plot” (Figure 3.1). 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 (Figure 3.1). This plot helps readers think about the reasons why there is wide variation in results among 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 among 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 among 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 3.1 clearly reflects this point, showing that the prevalence of postoperative pain varied considerably among 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 among 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 post-operatively 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 medications.
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. Walton & Fouad (1992), Imura (1995), and Eleazer & Eleazer (1998); its clinical significance as a differentiating factor between single- vs 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 guidelines 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 among 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 among studies reflects the widely varying measures of pain severity, differences in treatment protocols and patient selection, as well as variability in treatment effects.
Table 3.1: 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.

<table>
<thead>
<tr>
<th>No</th>
<th>Search history</th>
<th>Results</th>
</tr>
</thead>
</table>
Table 3.2: Inclusion and exclusion criteria used in the analysis

<table>
<thead>
<tr>
<th>Inclusion criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Subjects had a non-contributory medical history;</td>
</tr>
<tr>
<td>2. Subjects underwent non-surgical root canal treatment</td>
</tr>
<tr>
<td>3. There was comparison between single- and multiple-visit</td>
</tr>
<tr>
<td>4. Outcome was measured in terms of pain degree or</td>
</tr>
<tr>
<td>prevalence of flare-up.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Exclusion criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Pain was not measured at the completion of the</td>
</tr>
<tr>
<td>treatment;</td>
</tr>
<tr>
<td>2. No comparison between single- and multiple-visit</td>
</tr>
<tr>
<td>root canal treatment within the same study;</td>
</tr>
<tr>
<td>3. No data regarding prevalence of pain or flare-up;</td>
</tr>
<tr>
<td>4. No explicit details of endodontic clinical procedures</td>
</tr>
</tbody>
</table>
Table 3.3: Studies excluded from systematic review

<table>
<thead>
<tr>
<th>Excluded studies</th>
<th>Exclusion criteria (see Table 3.2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pekruhn (1986)</td>
<td>3</td>
</tr>
<tr>
<td>Friedman et al. (1995)</td>
<td>3</td>
</tr>
<tr>
<td>Soares &amp; Cesar (2001)</td>
<td>2</td>
</tr>
<tr>
<td>DiRenzo et al. (2002)</td>
<td>1</td>
</tr>
<tr>
<td>Siqueira et al. (2002)</td>
<td>2</td>
</tr>
<tr>
<td>Ghoddusi et al. (2004)</td>
<td>4</td>
</tr>
<tr>
<td>Oginni &amp; Udoye (2006)</td>
<td>4</td>
</tr>
</tbody>
</table>
### Table 3.4 Result summary of included studies

<table>
<thead>
<tr>
<th>Design</th>
<th>PA status</th>
<th>Sample size</th>
<th>Medication</th>
<th>Outcome measure</th>
<th>Raw data pain/total (S vs M)</th>
<th>Statistical result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eleazer &amp; Eleazer (1998)</td>
<td>Retrospective cohort</td>
<td>AP present</td>
<td>402</td>
<td>Metacresylacetate</td>
<td>Flare-up</td>
<td>6/201 vs 16/201</td>
</tr>
<tr>
<td>Ng et al. (2004)</td>
<td>Prospective cohort</td>
<td>AP present</td>
<td>405</td>
<td>Various medication</td>
<td>Postoperative pain</td>
<td>53/91 vs 113/324</td>
</tr>
<tr>
<td>Fava (1994)</td>
<td>Prospective cohort</td>
<td>AP absent</td>
<td>60</td>
<td>Calcium hydroxide</td>
<td>Postoperative pain</td>
<td>2/30 vs 1/30</td>
</tr>
<tr>
<td>Al-Negrish (2006)</td>
<td>RCT</td>
<td>AP absent</td>
<td>112</td>
<td>Calcium hydroxide</td>
<td>Postoperative pain</td>
<td>Not dichotomised</td>
</tr>
<tr>
<td>Gesi (2006)</td>
<td>RCT</td>
<td>AP absent</td>
<td>256</td>
<td>Calcium hydroxide</td>
<td>Postoperative pain</td>
<td>16/130 vs 9/126</td>
</tr>
<tr>
<td>O’Keefe (1976)</td>
<td>Prospective cohort</td>
<td>Mixed</td>
<td>132</td>
<td>Various medication</td>
<td>Postoperative pain</td>
<td>1/55 vs 7/77</td>
</tr>
<tr>
<td>Pekruhn (1981)</td>
<td>RCT</td>
<td>Not stated</td>
<td>102</td>
<td>Formocresol</td>
<td>Postoperative pain</td>
<td>11/51 vs 5/51</td>
</tr>
<tr>
<td>Mulhern (1982)</td>
<td>RCT</td>
<td>Not stated</td>
<td>60</td>
<td>No medication</td>
<td>Postoperative pain</td>
<td>8/30 vs 12/30</td>
</tr>
<tr>
<td>Oliet (1983)</td>
<td>Cohort*</td>
<td>Not stated</td>
<td>387</td>
<td>Not stated</td>
<td>Postoperative pain</td>
<td>28/236 vs 8/115</td>
</tr>
<tr>
<td>Roane (1983)</td>
<td>Prospective cohort</td>
<td>Mixed</td>
<td>359</td>
<td>Not stated</td>
<td>Postoperative pain</td>
<td>38/250 vs 34/109</td>
</tr>
<tr>
<td>Fava (1989)</td>
<td>Prospective cohort</td>
<td>Not stated</td>
<td>60</td>
<td>CMCP</td>
<td>Postoperative pain</td>
<td>1/30 vs 0/30</td>
</tr>
<tr>
<td>Walton (1992)</td>
<td>Prospective cohort</td>
<td>Mixed</td>
<td>935</td>
<td>No medication</td>
<td>Flare-up</td>
<td>5/196 vs 24/739</td>
</tr>
<tr>
<td>Imura (1995)</td>
<td>Prospective cohort</td>
<td>Mixed</td>
<td>1012</td>
<td>No medication</td>
<td>Flare-up</td>
<td>3/582 vs 13/430</td>
</tr>
<tr>
<td>Yoldas (2004)</td>
<td>RCT</td>
<td>Mixed</td>
<td>227</td>
<td>Calcium hydroxide + CHX</td>
<td>Flare-up</td>
<td>8/106 vs 2/112</td>
</tr>
</tbody>
</table>

N.S. = not statistically significant difference

*Not known whether prospective or retrospective.
Figure 3.1 L’Abbé plot of sixteen studies reporting prevalence of postoperative pain or flare-up in single- and multiple-visit root canal treatment.

1=Imura & Zuolo (1995); 2=O’Keefe (1976); 3=Eleazer & Eleazer (1998); 4=Walton & Torabinejad (1992); 5=Fava (1989); 6=Fava (1994); 7=Yoldas et al. (2004); 8=Al-Negrish & 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 & 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 twelve 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 (\( P > 0.05 \)).
REFERENCES:


Adverse effects

Dodge JS (1887) Immediate root filling Dental Cosmos 29, 234-5.


Adverse effects


Adverse effects


Patient perceptions of single- vs. multiple-visit root canal treatment: A randomized controlled clinical trial.

A manuscript prepared for submission to

*Health and Quality of Life Outcomes*

**Research Questions:**

Is single-visit root canal treatment more comfortable for patients than multiple-visit treatment?

Does patient prefer single- or multiple-visit root canal treatment and to what extent?
ABSTRACT

Single- vs multiple-visit root canal treatment has been the subject of a longstanding debate in the endodontic community. When clinicians are faced with choices of which treatment regimen to offer patients, the central issues that should be considered are effectiveness, complications, cost and patient/operator satisfaction and comfort. Patients and health-care professionals often have different views on and preferences for treatment because they look at treatment from different standpoints. A study of these views is important in delivering quality health care services because the modern philosophy of health care gives individuals greater autonomy in their treatment choices. This study aimed at systematically documenting patients’ perspectives on treatment (degree of discomfort) and patient preferences, as well as satisfaction with two alternative treatment regimens. The two treatment regimens were randomly assigned to patients who required root canal treatment on a molar tooth. Immediately upon completion of the treatment a self-administered questionnaire was completed, which was designed to capture differences in patients’ degree of discomfort, satisfaction and preferences between the two treatment regimens. Patients experienced little discomfort from the root canal treatment procedures and the overall degree of discomfort did not significantly differ between single- and multiple-visit treatment regimens. Patients strongly preferred single- over multiple-visit treatment. This study provides clinicians with useful information for making treatment decisions, and also allows a more complete evidence-based perspective on treatment options and delivery.
**INTRODUCTION**

Single- and multiple-visit root canal treatment has been the subject of long-standing debate in the endodontic community (Bergenholtz & Spångberg 2004). This controversy can be investigated more systematically with the aid of an evidence-based approach. The current best available evidence demonstrates no difference in therapeutic efficacy (healing rates) between these two treatment regimens in teeth with necrotic pulp and apical periodontitis (Sathorn *et al.* 2005, Figini *et al.* 2007, Ng *et al.* 2008). From an epidemiological point of view, complications (postoperative pain and flare-ups) of these two treatment approaches did not appear to be of great clinical importance. Flare-up is rare, averaging only approximately 3%; thus it lacks clinical impact, especially as a differentiating factor between the two treatment regimens. Again, compelling evidence of a significant difference in prevalence of postoperative pain/flare-up of either single- or multiple-visit root canal treatment is lacking (Figini *et al.* 2007, Sathorn *et al.* 2008).

Outcome measures have evolved from simple binary variables such as survival or occurrence of clinical events e.g. healing of apical periodontitis, to complex patient-oriented measures, ranging from functional disability scales to quality of life. The introduction of the patient’s point of view in quality and effectiveness studies can be considered a further step towards a more comprehensive humanistic approach to the patient who is seen as a ‘complex individual’ member of a dynamic community and not a ‘complex machine’ assembled with separate organ systems (Apolone & Mosconi 1998). ‘Complex individuals’
usually hold their own views of the world around them. A study of these views is important in delivering quality health care services.

Patients and health professionals often have different views on and preferences for treatment because they look at treatment from different standpoints. The direction and magnitude of these preference differences do not appear to be consistent and may vary with the clinical condition of interest (Montgomery & Fahey 2001). Modern philosophy of health care gives individuals greater autonomy in their treatment choices. It is a generally accepted idea that patients should have a say in treatment decision making (Montgomery & Fahey 2001), yet their perceptions of single- and multiple-visit root canal treatment have not been investigated. Information on patient perceptions, i.e. degree of discomfort during treatment, satisfaction, and preference between single- and multiple-visit root canal treatment would move us closer to a completed picture of these two competing alternative forms of treatment. This study aimed at systematically documenting patients’ perspectives on treatment (degree of discomfort) and patient preferences, as well as satisfaction with two alternative treatment regimens. This study will provide clinicians with another piece of crucial information when making a treatment decision and also allow a more complete evidence-based perspective on treatment options and delivery.

**MATERIALS AND METHODS**

**Patients**

The study received approval from the University of Melbourne Human Research Ethics Committee. We arbitrarily assumed that a 30% difference in choice of
preferred treatment regimen would be of clinical significance. A comparison of prevalence between two groups (e.g. 0.8 vs 0.5) at p<0.05 and 80% power would yield a number of 45 participants per group, hence 90 was the minimum sample size (Fleiss et al. 2003). Attrition was not expected because data were collected immediately after the completion of the treatment.

Participants were patients who required root canal treatment on a molar tooth and had been referred to the Specialist Endodontic Unit of the Royal Dental Hospital of Melbourne, Melbourne, Australia in the period 2005 to 2008. All patients were fully informed about the nature of the study including their random assignment to single- or multiple-visit treatment. Once they agreed to participate, a consent form was signed. Only patients with the following features were included in the study: 1) no previous root canal treatment in that particular tooth; 2) no preoperative technical complications e.g. ledge, fractured instrument, perforation; 3) asymptomatic tooth 4) relatively straightforward cases that could be completed in less than three hours.

**Treatment**

Seven operators provided the treatment. All were either endodontic specialists or residents in the Royal Dental Hospital of Melbourne, which provides low-cost treatment to low income patients and is the major teaching hospital for The University of Melbourne undergraduate and postgraduate dental clinics. Endodontic treatment procedures were uniform among operators, following generally accepted standards including the use of rubber dam. The root canal system was cleaned and shaped using rotary nickel-titanium (NiTi) instruments (ProTaper, ProFile-Dentsply International Philadelphia, USA and Flexmaster-
VDW GmbH Munich, Germany) within 0.5-1mm of the radiographic apex. The root canals were irrigated with 2.5% NaOCl. In multiple-visit cases, calcium hydroxide was placed as an inter-appointment medicament using either a lentulo-spiral or paste filler, and was left in the canal for at least one week (Sjögren et al. 1991). Root canals were obturated with a matched-tapered gutta-percha cone and an epoxy resin-based sealer using a lateral compaction technique.

**Survey instrument**

A written questionnaire was constructed based largely on previous quality of life studies in endodontics and oral surgery (Shugars et al. 1996, Dugas et al. 2002). This instrument was designed to capture differences in patient degree of discomfort, preferences and satisfaction between the two treatment regimens. The survey consisted of five questions plus space to provide written comments. Additionally, time spent on the treatment was recorded by the dental assistant. Two of the questions involved five or six different components to measure patient discomfort (e.g. mouth opening, neck or back pain) and satisfaction with treatment (expense, time, pain etc.). The assumption was made based on clinical experience that single-visit root canal treatment needs one longer visit to complete than each appointment of a multiple-visit approach. Questions were, therefore, designed to detect discomfort as a result of long appointments. Overall discomfort and treatment satisfaction were assessed using a modified visual analogue scale (Miller & Ferris 1993). The instrument was internally and externally validated prior to administration to patients. Cronbach’s coefficient was used to test validity of the instrument. This is a test based on the
correlations between different items on the same test (Table 4.1 and “Pleasantness” section in Table 4.2), and it measures whether several items that propose to measure the same general construct produce similar scores. The pilot study was performed on a small group of patients at the Royal Dental Hospital of Melbourne, resulting in minor adjustments. The instrument was given to the patient at the end of treatment; patients generally took around five minutes to complete the survey.

**Randomization**

CONSORT guidelines were strictly followed (Altman *et al.* 2001). All operators contributed at least one pair of patients (i.e., one in the single-visit group and the other in multiple-visit). Patients were taken off the waiting list and assigned to the operators by the hospital administrative staff who had no knowledge of the study. Patients had an equal probability of assignment to both treatments. The randomization code was developed using a computer random number generator to select random permuted blocks. In a small study the numbers allocated to each group may not be well balanced (Rosenberger & Lachin 2002). Hence, to maintain good balance, blocked randomization was used (Beller *et al.* 2002). Treatment allocation was concealed in a sealed envelope until patients who met the criteria for inclusion in the study were identified and agreed to participate. Single- or multiple-visit root canal treatment was strictly assigned according to the instruction in the envelope. Blinding was not possible for patients or operators.
Statistical methods

Differences in modified visual analog scales profiles were analyzed with Levene’s test for equality of variances and t-test for equality of means. Patient preferences for treatment regimen were analyzed using the Chi square test with Yates’ correction.

RESULTS

Cronbach’s coefficient based on correlations between the results in Table 4.1 and “Pleasantness” section in Table 4.2 was 0.65, which indicated acceptable reliability (Cronbach 1990, Leech et al. 2008).

Detailed discomfort

On a 0-4 scale (with 4 = severe discomfort), only one patient reported discomfort at level 3 and none at level 4 (Figure 4.1, question a). Other discomfort attributes (i.e., difficulty of mouth opening, aching of neck, back, jaw, and feeling claustrophobic) showed extremely low scores (Figure 4.1, question b-e), with a majority recording “0” in every category except aching of the neck, back or jaw. None of the detailed discomfort attributes showed a significant difference (p>0.05) between the two treatment regimens.

Overall discomfort

The overall degree of discomfort was low and did not significantly differ between the two treatment regimens (p=0.9) (Table 4.1). A substantial majority of patients reported none to mild discomfort (scores of 0-2 on a 10 point scale)
and only two reported substantial pain (8 and 10). Both were in the single-visit group and pain was encountered when the local anesthetic wore off.

**Satisfaction**

Patient perceptions of the two treatment regimens in terms of cost, time, pain, pleasantness, and satisfaction were not significantly different (p=0.6, 0.1, 0.4, 0.6 and 0.5 respectively) (Table 4.2). Both treatment regimens produced a very high average satisfaction score. More than 85% of patients from both treatment regimens recorded a satisfaction score of 8-10 (Table 4.2).

**Treatment regimen preference**

Overall, patients strongly preferred single- over multiple-visit treatment (74.1% vs. 25.9%). Treatment experience had a significant impact on patient treatment preference (p=0.009, Chi square with Yates’ correction). Patients who had experienced single-visit treatment were 4.6 times more likely to prefer single-visit treatment than patients who had experienced multiple-visit treatment (88.1% of single-visit patients expressed a preference for single-visit treatment and 61.7% of multiple-visit patients expressed a preference for single-visit treatment; Odds ratio = 4.6, 95%CI 1.6 to 13.3).

**Appointment length**

Actual time spent on the treatment was very different between the two treatment regimens. Mean time spent on single- and multiple-visit treatments were 163.3 ± 31.2 and 277.5 ± 67.6 minutes, respectively. In multiple-visit treatment, time spent on the first and second visits were 138.8 ± 30.9 and 138.7
+ 46.4 minutes, respectively, which are not markedly lower than the entire single-visit appointment length.

Treatment experience had a significant impact on patients’ willingness to tolerate long appointments (p=0.034). On average, patients who had had single-visit treatment were willing to tolerate around 14 minutes more than multiple-visit patients. A difference of this magnitude, however, might not be of clinical significance. Over all, 45% of patients were willing to tolerate up to 3 hours (Figure 4.2).

**DISCUSSION**

The measurement of intangible data *e.g.* pain, discomfort, and satisfaction is considered difficult, but not impossible (Layard 2005). Neurophysiological science confirms the objective character of pain by demonstrating the association of the experience reported by people and the measurements of brain activity by electroencephalogram or magnetic resonance imaging (Davidson 2000, Coghill *et al.* 2003). Thus, a link between what people report and objective brain activity has been established. There is no difference between what people think they feel and what they “really” feel. A modified visual analog scale is one of the accepted techniques to measure how people think they feel, and has been widely adopted and validated in pain research (Revill *et al.* 1976, Husemeyer *et al.* 1980, Mottola 1993). This scale can detect small differences in pain, is reliable, and is easy to administer.

Generally, patients had very little discomfort during the root canal treatment and were very satisfied with their experience. The number of patients who
found the experience exceedingly uncomfortable was very small (2/90), and was related to the local anesthetic wearing off (as reported in the comments section). Patients coped well with both treatment regimens and were very positive about the treatment received. The difference in treatment regimen had no impact on degree of discomfort. Both treatments have been standard clinical practice for a very long time. The longer appointment in single-visit treatment did not appear to affect patient discomfort. This might be explained by the fact that the difference was not great in actual appointment length of single-visit treatment and each visit of multiple-visit treatment (163.3 ± 31.2 vs 138.8 ± 30.9 and 138.7 ± 46.4).

A large majority of patients preferred single- over multiple-visit treatment regardless of their treatment experience (a three-fold difference). Patients might view dental visits as an unpleasant necessity (no matter how low the discomfort they actually experience) (Figure 4.1, Table 4.1), but they are willing to cope with it and prefer to get it over and done with.

It could be argued that patients cannot reliably judge which treatment they would prefer, when they have not experienced both. It is impractical to conduct a study where patients need treatment on two molar teeth at the same time. It is probably easier for single-visit patients to conclude that they would have preferred the treatment to be divided into two shorter visits, than the reverse. On the other hand, patients receiving treatment over two visits would be more likely to take traveling time and related non-treatment factors into account. Regardless of reasons (which were not explored in this short survey), both groups expressed a clear preference for single-visit treatment.
All treatments were provided in an Australian setting of treatment in a large institution (The Royal Dental Hospital of Melbourne) and with homogeneous patient pool (low income patients). Extrapolation of this study to other settings should be done with care, especially in relation to the time taken to complete treatment. In private practices, which are typically run more efficiently than a large institution, the appointment time could well be much shorter, rendering the degree of discomfort to be even smaller. It is, therefore, unlikely that the differences will become significantly apparent in private practices. Endodontic treatment is a skill-dependent procedure. Experienced operators are also likely to take less time to complete the same tasks compared to inexperienced ones.

In the USA, 90% of the health care budget is for curative treatment, around 9% is for prevention and only 1% is for patient quality of life (Porter & Teisberg 2006). These numbers paint a rather bleak picture of acknowledging the patient’s point of view in health care. Patient perceptions of treatment tend to be undervalued and generally neglected. In fact, they should be investigated and respected, as we are treating patients who hold their own values, feelings and preferences, which could very well be different from others and especially from operators (Montgomery & Fahey 2001). The patient’s point of view should be taken into account when formulating a treatment plan, particularly when two alternative forms of treatment provide similar outcomes.

**CONCLUSION**

Patients experienced little discomfort from root canal treatment procedures and the overall degree of discomfort did not significantly differ between single- and
multiple-visit treatment regimens. Patients strongly preferred single- over multiple-visit treatment.

ACKNOWLEDGEMENT

The authors gratefully acknowledge Associate Professor Dr Kanlaya Vanichbuncha of Department of Statistics, Faculty of Commerce and Accountancy, Chulalongkorn University, Thailand for her statistical expertise.
REFERENCES:


Figure 4.1 Detailed discomfort attributes

a) Did you feel faint or uncomfortable during or after the treatment?

b) How much difficulty do you have in opening your mouth after the treatment?

c) Did your neck, back or jaw ache during or after treatment?

d) Did the treatment make you feel claustrophobic?

e) Did you feel that the appointment was too long?

1=single-visit treatment 2=multiple-visit treatment

0=none and 4=extreme
Figure 4.2 Appointment length

Longest possible=the longest appointment patients were willing to tolerate

Longest preferred=if the patients could choose, this is the longest appointment they would prefer

1=single-visit treatment

2=multiple-visit treatment
### Table 4.1 Patients’ greatest degree of discomfort

<table>
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<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
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<td>1</td>
</tr>
<tr>
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<td>5</td>
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</tr>
</tbody>
</table>

Patients’ *greatest degree of discomfort during treatment*, based on a modified visual analog scale of 0-10, where a score 0 represents no discomfort and 10 the greatest imaginable degree of discomfort. Median score is shown in shaded cells. Data are based on 43 patients receiving single-visit treatment and 47 multiple-visit patients.
Table 4.2 Patients’ overall experience of root canal treatment

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</tr>
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<td></td>
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<tr>
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<tr>
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<td>Multiple</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Patients’ overall experience of root canal treatment, based on a modified visual analog scale of 1-10, where a score of 1 represents a highly unfavorable perception (e.g. very painful) and 10 a highly favorable perception (e.g. pain free). Median score is shown in shaded cells. Data are based on 43 patients receiving single-visit treatment and 47 multiple-visit patients.
5 CLINICAL FINDINGS: COST

Single- and Multiple-visit Root Canal Treatment: Cost-minimization Analysis

A manuscript prepared for submission to

Journal of Health Economics

RESEARCH QUESTION

Is single-visit root canal treatment less expensive than multi-visit treatment and, to what extent?
ABSTRACT

Apical periodontitis is a common dental disease with a high annual treatment cost. Single- and multiple-visit root canal treatments are two alternative forms of management of apical periodontitis. When clinicians are faced with choices of which treatment regimen to offer patients, the central issues that should be considered are effectiveness, complications, patient/operator comfort, preference and cost. The biological issues of treatment effectiveness, intra-operative discomfort, post-operative pain and flare-up of single- and multiple-visit endodontics have been studied, and no statistically significant differences have been demonstrated. This study compared the cost of the two forms of treatment. The data were collected based on treatment of 92 patients (45 single-visit, 47 multiple-visit) in the Royal Dental Hospital of Melbourne, Australia. The economic evaluation of choice was a cost-minimization analysis. The analysis was conducted from a societal perspective. Total cost of single- and multiple-visit treatment was AU$1710.50 and AU$2232.05 respectively. Instrument and material costs were minimal compared to labor and opportunity costs. Single-visit treatment costs society AU$ 522 less than multiple-visit treatment. This represented a cost saving of 23%. 

INTRODUCTION

Apical periodontitis is an inflammation of the tissue surrounding the root apex of a tooth, usually as a consequence of root canal infection. It is a common disease, and is managed by root canal treatment (or extraction). A weighted analysis of nine high quality epidemiological studies employing random sampling, showed apical periodontitis to be present in 46.1% of the total sample (2683 subjects) (Hansen & Johansen 1976, Allard & Palmqvist 1986, Eriksen et al. 1988, Odesjö et al. 1990, Eriksen & Bjertness 1991, Eriksen et al. 1995, Marques et al. 1998, Sidaravicius et al. 1999, Kirkevang et al. 2001). By extrapolation, almost half of the adult population will potentially have unmet endodontic treatment needs. An estimated 9.7 million endodontic treatments are performed annually in the USA (Manski & Brown 2007). The American Dental Association reported an average endodontic treatment fee in 1990 of US$417 (ADA 1994). Based on this figure and taking into account the inflation rate, the direct economic impact as a result of treatment fee in today’s dollar value is $6.4 billion annually. The indirect economic impact adds substantially to the direct costs, as these treatments require millions of dental visits and millions of days of lost work. The financial burden and economic impact to society of the treatment of such a highly prevalent disease is substantial.

The cost of health care is borne either by the individual directly or by insurance companies or government. The high cost of health care imposes constraints on access, whether funded by individuals or government. If expenditures can be minimized, more people will be covered, and more services will be provided...
(Muennig & Khan 2002). In other words, because resources are limited, every
time society uses scarce resources in one way, it gives up the opportunity to use
them in another way. Thus, there are broad health, social and economic
consequences of treatment choice, and potentially significant benefits
individually and collectively if it becomes possible to reduce the cost of
treatment. Policy makers and/or clinicians alike are, therefore, obliged to take
cost into consideration and choose the most cost-effective treatment, because
their treatment choices could potentially affect other parts of society.

Single- and multiple-visit root canal treatments are two alternative forms of
management of apical periodontitis. Single-visit root canal treatment is the
completion of cleaning, shaping and obturation in one appointment. Multiple-
visit root canal treatment is the completion of cleaning and shaping in the first
appointment, with obturation in a second (or later) visit. Antibacterial
intracanal medication is left in the canal for at least a week in between the two
appointments. The only difference between these two is the use of antibacterial
medication, which requires at least one week to work effectively (Sjögren et al.

The biological issues of treatment effectiveness, intra-operative discomfort,
post-operative pain and flare-up of single- and multiple-visit endodontics have
been studied, and no statistically significant differences have been
demonstrated (Sathorn et al. 2005, Figini et al. 2007, Ng et al. 2008, Sathorn et
The issue of cost is addressed in this study. As no significant difference in benefit and harm has been demonstrated, the economic evaluation of choice is a cost-minimization analysis, which will identify the less expensive regimen and the extent of the cost saving. The purpose of this paper is to present a cost-minimization analysis comparing the two clinical treatment regimens. This analysis is based on data from a recent randomized controlled clinical trial comparing patient experience with and preference for single- and multiple-visit root canal treatment (Chapter 4).

**MATERIALS AND METHODS**

The economic analysis of a randomized clinical trial was based on detailed information about health care resource utilization of each patient during treatment.

**The trial**

The trial received approval from the University of Melbourne Human Research Ethics Committee and the informed, written consent of all participants.

**Patients**

Participants were patients who required root canal treatment of a molar tooth and had been referred to the Specialist Endodontic Unit of the Royal Dental Hospital of Melbourne, Australia in the period 2005 to 2008. All patients were fully informed about the nature of the study including their random assignment to single- or multiple-visit treatment. Once they agreed to participate, a consent form was signed. Only patients with the following features were included in the
trial: 1) no previous root canal treatment in that particular tooth; 2) no preoperative technical complications e.g. ledges, fractured instruments, perforations; 3) asymptomatic tooth 4) relatively straightforward cases that could be completed in less than three hours. Patients had an equal probability of assignment to both treatments. The randomization code was developed using a computer random number generator to select random permuted blocks. In a small study the numbers allocated to each group may not be well balanced (Rosenberger & Lachin 2002). Hence, to maintain good balance, blocked randomization was used (Beller et al. 2002). The number of patients available for the economic analysis was 92: 45 patients from the single-visit treatment group and 47 from the multiple-visit treatment group. More specific details regarding the trial design and results are presented elsewhere (Chapter 4).

**Treatment**

Seven operators provided the treatment, with each operator providing both forms of treatment to different patients. Endodontic treatment procedures were uniform among operators, following generally accepted standards including the use of rubber dam. Canals were cleaned and shaped using rotary nickel-titanium (NiTi) instruments (ProTaper, ProFile-Dentsply International Philadelphia, USA and Flexmaster-VDW GmbH Munich, Germany) within 0.5-1 mm of the radiographic apex. Canals were irrigated with 2.5% NaOCl. In multiple-visit cases, calcium hydroxide was placed as an inter-appointment medicament using either a lentulo-spiral or paste filler, and was left in the canal for at least one week (Sjögren et al. 1991). Root canals were subsequently filled
with a matched-taper gutta-percha cone and an epoxy resin-based sealer using a lateral compaction technique.

**Data acquired**

Other than information on patient experience with and preferences between the two treatment regimens (Chapter 4), the trial also recorded patient traveling time and the time spent on each step of the treatment. This information was also used in the economic analysis. The patient information was obtained at the end of treatment and generally took some five minutes to complete. The economic evaluation assumed that the study groups were clinically similar.

**Economic analysis**

Data available for the economic analysis were as follows: 1) data acquired from the trial (time-related data); 2) cost of dental instruments and materials supplied by the Specialist Endodontic Unit of the Royal Dental Hospital of Melbourne (Table 5.1); 3) approximate life expectancy of instruments and major items of equipment (dental operating microscope, dental unit, etc.) obtained from practice managers of four private endodontic practices in Melbourne and Sydney, Australia; 4) endodontist and dental assistant salaries, overheads, and operating costs provided by Dental Health Services Victoria (the administrative body of the Royal Dental Hospital of Melbourne).

Opportunity cost was based on an average national wage rate (Muennig & Khan 2002). Private traveling cost was calculated using Australia’s most popular car model. The included expenses were standing costs (depreciation, interest, and registration), operating costs (fuel, tyres, and servicing) and parking fee as
advised by the Royal Automobile Club of Victoria (RACV). Public transport cost was calculated using ticket and operating costs. Environmental cost was based on CO$_2$ emission of the car model used in traveling cost calculation and Terrapass CO$_2$ offset cost scheme (Terrapass).

The analysis was conducted from a societal perspective which considers everyone affected by the treatment and counts all significant costs that flow from it, regardless of who experiences the outcomes or costs (Gold 1996). All costs were calculated based on 2008 data in Melbourne, Australia.

**RESULTS**

Table 5.2 summarizes the results of the economic analysis. A previous study (Chapter 4) reported the mean total single- and multiple-visit treatment time to be $163 \pm 31$ and $278 \pm 68$ minutes respectively, which were used to calculate the time-related cost elements. Based on the previous study, patients took on average 68 minutes to travel each way. Almost all of the cost differences can be attributed to total treatment time and traveling time. The large majority of costs were associated with labor costs, which in effect is associated with time. Instrument and material cost was AU$72.73 for single-visit treatment and AU$109.22 for multiple-visit treatment. These costs are minimal compared to labor and opportunity cost.

The total cost of single- and multiple-visit treatment was AU$1710.5 and AU$2232.05 respectively. Single-visit treatment thus costs society AU$ 522 less than multiple-visit treatment. This represented a cost saving of 23%.
DISCUSSION

Economic evaluation

Four tools are commonly used in economic evaluation of healthcare programs: cost-minimization, cost-effectiveness, cost-utility, and cost-benefit analysis. They differ only in the way that benefits are measured: costs are measured in exactly the same way in all methods (Buck 2000). Cost-minimization analysis was chosen in this study because effectiveness and adverse effects of the two treatments have been shown not to be significantly different (Sathorn et al. 2005, Figini et al. 2007, Sathorn et al. 2008, Ng et al. 2008, de Chevigny et al. 2008). Direct, indirect and intangible costs were all included. Discounting (a calculation that takes into account inflation rate or depreciation of money value over a period of time) was not performed because the analysis was done at a single point in time.

Because different analysis perspectives require including or excluding different costs, the only way to standardize an economic analysis is to require that all analyses assume the same perspective. The reference case scenario of the Panel on Cost-Effectiveness in Health and Medicine requires that the societal perspective be adopted (Gold 1996), and hence it was chosen for this analysis.

Study premises vs. Private practices

All treatments were provided in a large institution (The Royal Dental Hospital of Melbourne), with a homogeneous patient pool (low income patients). All staff are salaried, at rates below private practice earnings. Treatment fees (out-of-pocket fee plus government subsidy) were lower than the private practice fee by
approximately one half. Extrapolation of the results of this study to other settings thus should be done with care, especially in relation to the time taken to complete treatment and the labor cost. Anecdotally, private practices are typically run more efficiently than a large institution; the treatment time could well be much shorter, possibly rendering the time and cost saving to be smaller. On the other hand, the labor cost and treatment fee in private practice are higher. Endodontic treatment is a skill-dependent procedure. Experienced operators are also likely to take less time to complete the same tasks compared to inexperienced operators.

The patient opportunity cost was calculated using the average national wage, which was representative of patients in the study setting. Patients in private practices, however, are likely to earn and economically contribute more to society in terms of productivity. The opportunity cost for this group of patients is, therefore, potentially higher and the percent cost saving could be higher as a result.

As a public benevolent institution, the Royal Dental Hospital of Melbourne enjoys heavily subsidized prices for materials and supplies from dental supply companies. These costs are higher when purchased by private practices. Regardless of the instrument and material cost differences, the percentage cost saving between the two treatment regimens would be roughly the same because the major contributors to the cost difference are not instruments and materials (AU$72.73 vs AU$109.22), but rather labor and opportunity cost (AU$427.75 vs AU$746.57).
Impact on society at large

Patients frequently wait up to two years to receive definitive treatment in the Specialist Endodontic Unit at the Royal Dental Hospital of Melbourne. The delay results from the limited government resources allocated to specialist dental care. This long waiting period could have undesirable effects on patient general and oral health. If the treatment time can be better utilized, such as routinely aiming for single-visit root canal treatment when technically and biologically feasible, the waiting time could be potentially shortened by up to one half. Also society would be financially better off by up to one quarter. This would increase service coverage, and financially disadvantaged patients would greatly benefit from such a change.

Worst case analysis and hypothetical cost-effectiveness analysis

Assuming that any failed single-visit treatment would be managed by conservative retreatment using a multiple-visit approach, a worst case analysis can be conducted. From a societal perspective, routinely performing single-visit treatment when technically and biologically possible will make financial sense unless the difference in clinical outcome (healing) is more than 18.7% in favor of multiple-visit treatment. Three meta-analyses of the effectiveness of single- and multiple-visit root canal treatment have shown that there is only a 2.5% chance (based on the upper 95% confidence limit) that there exists a difference in healing larger than 7.8% in favor of multiple-visit treatment (Sathorn et al. 2005, Figini et al. 2007, Ng et al. 2008). In other words, considering costs and treatment effectiveness in a worst-case scenario, it is extremely unlikely that society will benefit economically or otherwise if multiple-visit treatment is
performed routinely. On the other hand, based on the lower 95% confidence limit, there is the same 2.5% chance that single-visit treatment has 20.3% higher healing (Sathorn et al. 2005, Figini et al. 2007, Ng et al. 2008).

It could be argued that the treatment time from the clinical trial (Chapter 4), which formed the basis for economic analysis and was the major cost driver, was unrealistically long (163 vs 278 minutes, a 41% time saving). When the economic analysis was repeated using hypothetically more moderate and more realistic figures (i.e. 90 vs 120 minutes, a 25% time saving), the results (16.4% cost saving) were not substantially different from the analysis using the actual numbers (23% cost saving). With these hypothetically more realistic figures, routinely performing single-visit treatment when technically and biologically possible makes financial sense unless the difference in healing is more than 14.1% in favor of multiple-visit treatment, which is again extremely unlikely.

**SUMMARY**

Base on the analysis, single-visit root canal treatment is much more cost effective given equal clinical outcomes and equal risk of adverse effects. Single-visit root canal treatment should be favored as a treatment choice when technically and biologically feasible. Especially for government or insurance funded institutions, it seems logical to adopt single- over multiple-visit root canal treatment.
Table 5.1 Clinical costs

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<td><strong>109.22</strong></td>
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</tbody>
</table>

See appendix for detailed cost breakdowns
## Table 5.2 Overall Cost

<table>
<thead>
<tr>
<th>Costs</th>
<th>Single visit treatment cost</th>
<th>Multiple-visit treatment cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical cost (Table1)</td>
<td>72.73</td>
<td>109.22</td>
</tr>
<tr>
<td>Salaries</td>
<td>281.65</td>
<td>478.4</td>
</tr>
<tr>
<td>Patient-related*</td>
<td>1171.11</td>
<td>1293.17</td>
</tr>
<tr>
<td>Overheads (DHSV)</td>
<td>62.51</td>
<td>106.16</td>
</tr>
<tr>
<td>Other**</td>
<td>122.55</td>
<td>245.10</td>
</tr>
<tr>
<td><strong>Grand Total</strong></td>
<td><strong>1710.5</strong></td>
<td><strong>2232.05</strong></td>
</tr>
</tbody>
</table>

See appendix for detailed cost breakdowns

* Out-of-pocket treatment fee, traveling expenses

** Opportunity cost
REFERENCES:


RACV


6 ADOPTION OF CHANGE: ENDODONTISTS’ PERCEPTIONS

Endodontists’ perceptions of single- and multiple-visit root canal treatment.

A manuscript submitted for publication in the

International Endodontic Journal

RESEARCH QUESTIONS:

Is single-visit root canal treatment more comfortable to perform than multiple-visit treatment?

Do endodontists prefer single- or multiple-visit root canal treatment as the standard clinical procedure?
ABSTRACT

Aim: To ascertain endodontists’ point of view (treatment philosophy, rationale, and preference) regarding single- and multiple-visit root canal treatment. To identify the basis on which the choice is made and how the information necessary for the choice is acquired.

Methodology: Endodontists registered with the dental practice board of every state in Australia were contacted, and if they agreed to participate, were interviewed either face-to-face or by telephone. The following topics were addressed in an interview lasting 15 to 20 minutes: demographics, current clinical procedures, treatment rationales and preference. A hypothetical scenario was posed to investigate which treatment regimen they would prefer to deliver if biological concerns were eliminated from consideration.

Results: Fifty two endodontists (71% of all Australian endodontists) agreed to participate in the study. Almost all (51/52) participants had performed single-visit root canal treatment, but very few routinely (2/52) performed it. A majority of participants were willing to provide single-visit treatment where patients had time constraints, and in vital cases (including elective endodontics). The most powerful factor influencing practice change was interpersonal contact with colleagues. The weakest influence in practice change was publications in academic journals.

Conclusions: Australian endodontists strongly prefer multiple-visit over single-visit root canal treatment even in cases where biological concerns are not
Endodontists’ perceptions

an issue. Operator preference rather than biological or patient considerations appears to be the primary determinant of treatment choice.
Introduction

Single- and multiple-visit root canal treatment has been the subject of long-standing debate in the endodontic community (Bergenholtz & Spångberg 2004). It has been established that the current best available evidence has failed to demonstrate a difference in therapeutic efficacy (healing) between these two treatment regimens (Sathorn et al. 2005, Figini et al. 2007, Ng et al. 2008), while patients strongly prefer it (Chapter4). Also, compelling evidence is lacking of a significantly different prevalence of postoperative pain/flare-up of either single- or multiple-visit root canal treatment (Figini et al. 2007, Sathorn et al. 2008).

Another important consideration in treatment decision-making is the human factor. Clinicians have a strong influence on treatment decision-making; in many circumstances they are more influential than any other parties in the treatment decision. Anecdotally, endodontists are not likely to offer patients a choice between single- and multiple-visit treatments other than in exceptional circumstances because of their clinical perceptions including treatment philosophy, rationale, and preference for the different treatment options. Furthermore, root canal treatment is a skill-dependent procedure, therefore, operator skill, preference, comfort and convenience could also affect the choice of treatment.

The adoption of new treatments, techniques or concepts depends not only on their effectiveness or biological rationale, but also on operator preference for, and satisfaction in, performing such procedures (Granados et al. 1997). Some
clinical procedures are not widely implemented for the simple reason that they are too difficult or too inconvenient to perform, even though they have a strong biological rationale. Infrequent use of rubber dam is the classic example in endodontics. Undoubtedly biological principles of endodontic treatment are violated when rubber dam is not used, yet a majority of practitioners continue to practise in such a manner (Whitworth et al. 2000, Slaus & Bottenberg 2002, Wilson et al. 2004, Björndal & Reit 2005).

Decision making by clinicians appears to be complex and multidimensional. Treatment effectiveness and complications are only two of several important factors in the decision making process, and social, psychological and even economic factors are also likely to play roles in the treatment decision (Greenhalgh et al. 2004). Also, clinical behavioural modification can only take place when there is a full understanding of what distracts clinicians from biologically sound treatment procedures. Merely providing scientifically valid information does not appear sufficient to lead to sustained behaviour change in practice (Davis et al. 1995, Stanton & Grant 1997).

This interview-based study aimed at identifying issues that influence treatment decisions from the operator point of view, by exploring endodontists’ perspectives on single- and multiple-visit treatment approaches. Attempts were also made to identify the basis on which the choice is made and how the information necessary for the choice is acquired. By surveying a substantial majority of all endodontists in Australia, a broadly national perspective on the issue was sought.
MATERIALS AND METHODS

The study received approval from the Health Sciences Human Research Ethics Committee, of the University of Melbourne, Australia. All endodontists registered with the dental practice board of every state in Australia were contacted, and if they agreed to participate, were interviewed either face-to-face or by telephone. The two interview methods are considered equivalent as a research methodology (Holstein & Gubrium 2002). The interview format was semi-structured with a predetermined set of questions, which were similarly applied to all interviewees. The following topics were addressed in an interview lasting 15 to 20 minutes: demographics, current clinical procedures, treatment rationales and preference. Scripted questions were asked in a strictly non-leading manner to encourage interviewees to answer freely. Different options to choose from in answering questions were not given in any way; all the answers were initiated and volunteered by interviewees. A hypothetical scenario was posed to investigate which treatment regimen they would prefer to deliver if biological concerns were eliminated from consideration. The answers were recorded, transcribed, and entered into spreadsheet software for analysis.

RESULTS

Demographics and current clinical procedures

Fifty two endodontists agreed to participate in the study i.e. 71% of registered Australian endodontists. All participants were in private practice, with most having been in specialist practice for more than ten years (Table 6.1). A large majority were Australian trained. The non-responder demographics are shown
in Table 6.1. Non-responder numbers seemed to be distributed randomly among the different states.

Clinical procedures were rather similar among interviewees. All but one endodontist used rotary NiTi instruments for canal preparation. For those who used rotary NiTi, a wide variety of NiTi systems were used, but all were used in a crown-down manner. Twenty eight endodontists used a matched-taper cone hybrid technique to obturate canals, ten used warm vertical compaction and nine traditional lateral compaction.

Sixty four percent of participants (33/52) had a separate consultation visit, typically of 30 minutes or less, before beginning definitive treatment. Standard treatment visits were typically 90 minutes or less (27/52 operators) (Figure 6.1). The majority of participants (32/52) estimated that they took or would take more than 90 minutes to complete a straightforward molar tooth in one visit (Figure 6.2).

**Single- vs Multiple-visit treatment**

All but one participant had performed single-visit root canal treatment, but very few routinely performed it. In fact, only one endodontist exclusively performed single-visit, one never did, and the remainder rarely did. A majority of participants were willing to provide single-visit treatment where patients had time constraints, and in vital cases (including elective endodontics). Other situations where single-visit treatment was considered appropriate were rarely mentioned (Table 6.2).
Endodontists’ perceptions

The most commonly volunteered reasons for not performing single-visit treatment were related to canal infection and microbial control [need for medication (36/52), teeth with apical periodontitis (16/52)], then pain and flare-up; then operator factors (Table 6.2).

Most participants (41/52, 79%) did not offer patients a choice of treatment regimen. In technical terms, the majority of participants hold a paternalistic (authoritative) approach to treatment decision making (Hunink 2001).

**Preference if biological concerns were resolved**

A hypothetical situation was posed in which bacterial elimination could be reliably achieved in a single-visit. With this scenario a majority of participants (37/52) indicated a preference for single-visit treatment, most of whom stated that “patients prefer it”. There was a range of reasons for single-visit preference, which could be grouped into three categories i.e. patient factors (27/52), endodontist factors (20/52) and other reasons (1/52) (Table 6.3). Twenty five percent of participants would continue to prefer multiple-visit root canal treatment even if all biological constraints could be removed from the decision-making equation, of whom half regarded it as physically more comfortable for the endodontist. Two participants rejected the scenario as an impossible situation.

**Openness to change/innovation**

All participants offered reading journals as a way to keep pace with current developments in endodontics, followed by attending meetings (40/52) and discussion with colleagues (32/52) (Table 6.4). Forty three participants
identified the operating microscope as a major change in endodontics since their graduation, and 41 nominated rotary NiTi files. No other innovation was mentioned by more than four respondents. The most powerful method of influence in practice change was interpersonal contact with colleagues: half of the participants adopted the use of the operating microscope because of informal discussion with colleagues (Table 6.4). The weakest influence in practice change was publications in academic journals; only one endodontist cited reading journals as a reason why he changed the way he practises.

**DISCUSSION**

**Study method and limitations**

A high response rate from any sample is essential for the data to be representative of the entire population (Fink 2003). Opinions differ as to a response rate high enough to eliminate nonresponse bias, but the range reported is commonly 70-80% (Gough & Hall 1977, Evans 1991, Christie et al. 1997). Our response rate (71%) was within this range. An interview method was chosen over a written questionnaire because it is a two-way communication and reduces the likelihood of misinterpretation. An interview allows deeper exploration of issues as they come up in the process.

Generalizability of this study may be limited, as it represents only Australian endodontists’ views. Practitioners in other parts of the world will have different educational background, practice philosophy and belief systems. One survey demonstrated that in the US almost 70% of endodontists would treat teeth with a necrotic pulp and chronic apical abscess in one visit (Whitten et al. 1996),
which is completely different from the finding (6%) in this study (Table 6.2). Nonetheless, the study provides insights into the way specialists acquire information and use it in treatment decision-making.

**Range of treatment philosophy**

The major concern of participants who preferred a multiple-visit approach was bacterial control and management of infected canals. Many interviewees felt strongly that bacterial control could be maximized only with calcium hydroxide medication, even though the current best available evidence does not support such a notion (Sathorn et al. 2007a).

In addition, participants tended to rely on bacterial culture studies as the biological rationale for their treatment decision-making process. The issue of treatment effectiveness (healing) of single- and multiple-visit root canal treatment was mentioned by only two participants. This finding suggests that participants considered the results of bacterial culture studies as the “gold standard” by which any treatment regimen should be measured. Bacterial culturing is at best a surrogate endpoint for clinical outcome (healing) (Prentice 1989, De Gruttola et al. 2001, Sathorn et al. 2007b), and numerous studies have shown that negative cultures are not reliably achieved following cleaning and shaping procedures. The same, however, is true following intracanal medication, and the frequency of positive cultures may be similar or even greater after the use of medicaments (Peters et al. 2002, Zerella et al. 2005, Sathorn et al. 2007a). Logically, studies of the true end point (healing) should be more meaningful and more relevant to the treatment decision. Studies of healing have consistently documented the absence of any difference between
single- and multiple-visit treatment (summarized in (Sathorn et al. 2005, Figini et al. 2007, Ng et al. 2008). It must be acknowledged, however, that the reliability of clinical data on healing has been questioned (Spångberg 2007), with strong advocacy of the continuing need for intracanal medicaments (Spångberg 2001, Nair et al. 2005).

The treatment decision depends not only on scientific principles, but also on social and psychological dimensions. It was clearly shown that some operators preferred a multiple-visit approach even in cases where bacterial control is not an issue (specifically, vital cases). Therefore, the actual reason for the preference for multiple-visit treatment must have been something other than bacterial control e.g. practice management, operator convenience, or simply habit. In fact, there were discrepancies between the time taken to complete endodontic treatment of a molar tooth in a single visit and the longest appointment time participants were willing to offer patients. Single-visit root canal treatment in a molar tooth generally took longer than the majority of participants were willing to offer (Figure 6.1 and Figure 6.2).

When reasons such as “peace of mind” or “feeling uncomfortable” were given, participants were questioned further for the reasons behind it. The commonly mentioned fear of flare-up may reflect a risk-averse approach to practice, even though the concern may be misplaced (Figini et al. 2007, Sathorn et al. 2008).
Adoption of change

The results of this survey provide insights concerning the adoption of change in specialist practice: firstly, how specialists keep pace with developments in their field; and secondly, how they actually incorporate innovation in their practice.

The three main methods that the respondents identified for keeping up-to-date with developments in endodontics were through reading journals (52/52), attendance at meetings (40/52) and through interaction with colleagues (32/52). Other means were rarely mentioned (Table 6.4). In a different part of the interview, respondents were also asked what they saw as the major developments in endodontics during their own careers and how they had acquired their knowledge of these developments. A very different picture emerged. No one source was nominated by a majority of respondents, and the three main sources of information were through colleagues (24/52), from personal evaluation of the new procedure (19/52) and via attendance at professional meetings (14/52). This pattern is in accordance with previous medical and dental literature (Coleman et al. 1957, Parashos & Messer 2006) that subjective personal experiences of professional peers with a new technology or procedure were more important than scientific data in convincing practitioners to change. Only one person nominated journals as the source of information influencing the decision to adopt a new procedure. In this context, journals may represent the primary source of scientific data in relation to new developments, but are insufficient to promote actual change in clinical practice.

The role of opinion leaders in promoting change has received a great deal of attention in the medical literature and to a lesser extent in the dental literature.
Specialists are often seen by general practitioners to be opinion leaders (Blumberg 1999, David 2000, Robertson et al. 2001). Among specialists, however, peer influence is more likely to occur. One of the recently developed learning theories is “community of practice” (Hughes et al. 2007). Rather than defining learning as the acquisition and internalization of knowledge, in this theory, learning is considered as a process of becoming a member of a sustained community of practice. Communities of practice are groups of people who informally bind together, share a concern, set of problems, or a passion about a topic, and who deepen their knowledge and expertise in this area by interacting on an ongoing basis (Wenger et al. 2002). This learning theory seems to fit better than the opinion-leader concept and has more influence in practice change in a specialist setting than conventional forms of learning e.g. lectures, journal reading, etc. A community of practice may serve to restrain change as well as promote it. Almost all Australian endodontists (50/52) surveyed rarely practised single-visit treatment even in instances where they acknowledge its benefits. This is in contrast to the US, where single-visit treatment has been widely practised.

**Resistance to change**

Despite a growing body of evidence on the issues of single- vs multiple-visit root canal treatment (Sathorn et al. 2005, Sathorn et al. 2007a, Figini et al. 2007, Sathorn et al. 2008, Ng et al. 2008), in some circles single-visit root canal treatment is not yet considered an accepted procedure, and waiting for more information before adopting the practice would be considered prudent.
The resistance to change is well illustrated in this survey. Despite the evidence supporting the biological rationale for single-visit treatment in vital cases, and endodontists’ recognition of lower costs and patient preference, a very large majority of participants (50/52) nevertheless rarely perform single-visit treatment. This resistance to change, however, is far from isolated. The adoption of new ideas, techniques or changes does not occur naturally. It is in fact more natural for human beings to resist change (Hultman 1998). The theory of adoption of innovation offers several explanations why participants seemed reluctant to change their practices to accommodate single-visit treatment (Rogers 2003). Firstly, the current best available evidence on the issues of single- vs multiple-visit root canal treatment might not coincide with the participant’s current values, beliefs, and attitudes. Secondly, they may not perceive that the benefits and rewards for making the change outweigh the trouble involved (i.e., the change threatens to modify established working patterns). Thirdly, a demonstrated need for the change does not appear to exist.

**CONCLUSIONS**

Australian endodontists strongly prefer multiple-visit over single-visit root canal treatment even in cases where biological concerns are not an issue. Operator preference rather than biological or patient considerations appears to be the primary determinant of treatment choice.
### Table 6.1 Details of survey participants

<table>
<thead>
<tr>
<th>Number of years in specialist practice</th>
<th>Number of participants</th>
<th>Specialist training in</th>
<th>Number of participants</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 10</td>
<td>18</td>
<td>Australia</td>
<td>39</td>
</tr>
<tr>
<td>11 to 20</td>
<td>21</td>
<td>Overseas</td>
<td>12</td>
</tr>
<tr>
<td>≥ 21</td>
<td>12</td>
<td>No formal training</td>
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</tr>
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</table>

<table>
<thead>
<tr>
<th>State</th>
<th>Number of non-responders</th>
</tr>
</thead>
<tbody>
<tr>
<td>Australian Capital Territory</td>
<td>2</td>
</tr>
<tr>
<td>New South Wales</td>
<td>6</td>
</tr>
<tr>
<td>Queensland</td>
<td>5</td>
</tr>
<tr>
<td>South Australia</td>
<td>3</td>
</tr>
<tr>
<td>Victoria</td>
<td>2</td>
</tr>
<tr>
<td>West Australia</td>
<td>3</td>
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</tbody>
</table>
Table 6.2 Clinical scenarios and treatment rationales

Various scenarios where participants indicated that single-visit treatment can and cannot be performed, and rationales for multiple-visit treatment.

<table>
<thead>
<tr>
<th>SV Possible</th>
<th>N</th>
<th>SV not possible</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vital</td>
<td>34</td>
<td>Symptomatic</td>
<td>25</td>
</tr>
<tr>
<td>Time constraints</td>
<td>30</td>
<td>Tooth with AP</td>
<td>16</td>
</tr>
<tr>
<td>Asymptomatic</td>
<td>4</td>
<td>Canal cannot be dried</td>
<td>16</td>
</tr>
<tr>
<td>Draining sinus</td>
<td>3</td>
<td>Necrotic</td>
<td>15</td>
</tr>
<tr>
<td>Single canal</td>
<td>3</td>
<td>Infected</td>
<td>13</td>
</tr>
<tr>
<td>Every situation</td>
<td>2</td>
<td>Retreatment</td>
<td>13</td>
</tr>
<tr>
<td>No circumstances</td>
<td>1</td>
<td>Draining sinus</td>
<td>12</td>
</tr>
<tr>
<td>Non vital without AP</td>
<td>1</td>
<td>Large area</td>
<td>8</td>
</tr>
<tr>
<td>Canal can be dried</td>
<td>1</td>
<td>Grossly infected</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Multi canal</td>
<td>1</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Rationales for multiple-visit treatment</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bacterial control</td>
<td>36</td>
</tr>
<tr>
<td>Pain</td>
<td>20</td>
</tr>
<tr>
<td>Dentist feels more comfortable (no science)</td>
<td>18</td>
</tr>
<tr>
<td>Want to see it settle or sign of healing</td>
<td>4</td>
</tr>
<tr>
<td>Wet canal cannot seal</td>
<td>3</td>
</tr>
<tr>
<td>More comfortable for patient</td>
<td>2</td>
</tr>
<tr>
<td>Better technical quality in multiple</td>
<td>2</td>
</tr>
<tr>
<td>SV is less successful</td>
<td>2</td>
</tr>
<tr>
<td>Multiple visit gives good result why change</td>
<td>1</td>
</tr>
</tbody>
</table>

SV = single-visit treatment

AP = apical periodontitis


<table>
<thead>
<tr>
<th></th>
<th>Single-visit</th>
<th>N</th>
<th>Multiple-visit</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Patient factors</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patient prefer it</td>
<td>14</td>
<td></td>
<td>Patient comfort</td>
<td>4</td>
</tr>
<tr>
<td>Lower cost</td>
<td>10</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Less time off work</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fewer injections (local</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>anesthetic)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>More comfortable for patient</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Endodontist factors</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>More efficient</td>
<td>12</td>
<td></td>
<td>Operator comfort</td>
<td>7</td>
</tr>
<tr>
<td>Operator prefers it</td>
<td>4</td>
<td></td>
<td>Peace of mind</td>
<td>1</td>
</tr>
<tr>
<td>More profitable</td>
<td>3</td>
<td></td>
<td>Easier to collect fee</td>
<td>1</td>
</tr>
<tr>
<td>Less writing (reports)</td>
<td>1</td>
<td></td>
<td>Get to know patient</td>
<td>2</td>
</tr>
<tr>
<td><strong>Other (biological)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Less leakage (interim</td>
<td>1</td>
<td></td>
<td>Better technical quality</td>
<td>3</td>
</tr>
<tr>
<td>restoration)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Table 6.4 Methods by which endodontists update their knowledge, and methods of influence in practice change

<table>
<thead>
<tr>
<th>Method of keeping up-to-date</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>Journal</td>
<td>52</td>
</tr>
<tr>
<td>Meeting</td>
<td>40</td>
</tr>
<tr>
<td>Colleagues</td>
<td>32</td>
</tr>
<tr>
<td>Teaching</td>
<td>5</td>
</tr>
<tr>
<td>Internet</td>
<td>1</td>
</tr>
<tr>
<td>Being a reviewer</td>
<td>1</td>
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</table>

<table>
<thead>
<tr>
<th>Reasons for change</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colleagues</td>
<td>24</td>
</tr>
<tr>
<td>Personal experience</td>
<td>19</td>
</tr>
<tr>
<td>Professional meeting</td>
<td>14</td>
</tr>
<tr>
<td>Hands-on training</td>
<td>10</td>
</tr>
<tr>
<td>Dental company recommendation</td>
<td>1</td>
</tr>
<tr>
<td>Journal</td>
<td>1</td>
</tr>
</tbody>
</table>
Figure 6.1 Appointment time (mins) that endodontists were willing to offer patients
Figure 6.2 Single-visit treatment time

The time endodontists believe they can complete endodontic treatment in a straightforward molar tooth.
REFERENCES


Endodontists’ perceptions


7 A CONFLICT IN DECISION-MAKING PHILOSOPHY: BIOLOGICAL ASPECT

Antibacterial efficacy of calcium hydroxide intracanal dressing: a systematic review and meta-analysis.

A manuscript published in


**RESEARCH QUESTION:**

Is single-visit root canal treatment more effective in bacterial elimination than multiple-visit, and to what extent?
Abstract

**Aim** To determine the extent to which calcium hydroxide intracanal medication eliminates bacteria from human root canals, compared to the same canals before medication, as measured by the number of positive cultures, in patients undergoing root canal treatment for apical periodontitis (teeth with an infected root canal system).

**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 studies were pre-test/post-test clinical trials comparing the number of positive bacterial cultures from treated canals. Data in those studies were independently extracted. Risk differences of included studies were combined using the generic inverse variance and random effect method.

**Results** Eight studies were identified and included in the review, covering 257 cases. Sample size varied from 18 to 60 cases; six studies demonstrated a statistically significant difference between pre-medicated and post-medicated canals, whilst two did not. There was considerable heterogeneity among studies. Pooled risk difference was -21%; 95% CI: -47% to 6%. The difference between pre-medication and post-medication was not statistically significant (p=0.12).
Conclusion Calcium hydroxide has limited effectiveness in eliminating bacteria from human root canals when assessed by a culture technique.
INTRODUCTION

Calcium hydroxide has been used in dentistry for almost a century (Siqueira Jr & Lopes 1999). Its use in root canal treatment as an intracanal medication has been associated with periradicular healing (Sjögren et al. 1990) and few adverse reactions (De Moor & De Witte 2002). Its use in root canal treatment was promoted by a series of papers (Byström et al. 1985, Byström & Sundqvist 1985) documenting the antibacterial efficacy of calcium hydroxide in human root canals. Subsequent studies substantiated these reports (Ørstavik et al. 1991, Sjögren et al. 1991), and the routine use of calcium hydroxide as an interappointment intracanal medicament become widespread.

Apical periodontitis is caused by bacteria within the canal space (Kakehashi et al. 1965, Möller et al. 1981). The treatment of apical periodontitis should, therefore, aim at bacterial eradication. Because cleaning and shaping procedures alone do not reliably eliminate bacteria (Byström & Sundqvist 1981, Dalton et al. 1998), it seems logical to medicate canals with an antibacterial agent after canal preparation. Recently, the ability of calcium hydroxide medication to eradicate completely bacterial species from the root canal has been questioned. For example, ex vivo studies have shown that dentine can inactivate the antibacterial activity of calcium hydroxide (Haapasalo et al. 2000, Portenier et al. 2001) and one clinical study (Peters et al. 2002) has shown that the number of bacterial positive canals increased after calcium hydroxide medication. Other studies have indicated that calcium hydroxide could not reliably eliminate bacteria or that some cultures changed from negative to

When different studies report inconsistent results, a systematic review and meta-analysis technique can clarify conflicting research data and the current state of knowledge regarding specific issues. A systematic review is a method of systematically identifying relevant research, appraising its quality and synthesizing the results (Glasziou 2001). Such a review of the antibacterial efficacy of calcium hydroxide has been conducted (Law & Messer 2004); however, since its publication, there have been three further clinical studies published that provide more complete information on culture results. In addition, the previous review did not perform a meta-analysis, on the grounds that the level of evidence was too low for such an analysis to be of value.

The ideal clinical question to be answered in this systematic review can be framed in terms of a PICO question [problem (P), intervention (I), comparison (C), and outcome (O)] as follows: In patients undergoing endodontic treatment for apical periodontitis, does an intracanal medicament, compared to no intracanal medicament, result in elimination of bacteria from the root canal system, as measured by a negative culture? Only one of the eight studies evaluated included a control group (no intracanal medication), on the premise that bacteria multiply rapidly when canals are left empty between appointments (Byström & Sundqvist 1981, Byström et al. 1985, Yoshida et al. 1995). Thus, it was necessary to restate the question to compare the bacterial status of the same canals before and after medication: In patients undergoing root canal treatment for apical periodontitis (teeth with an infected root canal system), to what extent
does calcium hydroxide medication eliminate residual bacteria from human root canals, compared to the same canals before medication, as measured by the number of positive cultures?

Most clinical studies sample canals for bacterial culture at three stages: 1) after initial access, to confirm that the canal is infected at the time of treatment (designated S1); 2) after the cleaning and shaping procedure is complete, immediately before canal medication (S2); 3) when the canal is re-accessed 1-4 weeks later, after the medication has been removed (S3). Teeth with apical periodontitis (as manifested by a periapical radiolucency) routinely have an infected root canal system; hence S1 is positive in essentially 100% of cases (Sundqvist 1976). Canal debridement (cleaning and shaping) results in an extensive reduction in bacterial count (99-99.9%) and in most studies a substantial proportion of negative cultures has been reported at S2 (0 - 86%, pooled mean 38% in the review by Law & Messer 2004). It has been shown that calcium hydroxide could interfere with the validity of microbiological sampling (Reit et al. 1999). To take this issue into account, ideally, teeth with negative cultures at S2 should be tracked separately from those with positive cultures in assessing the effectiveness of calcium hydroxide as measured at S3. This information was generally lacking in the studies reviewed by Law & Messer (2004). For this meta-analysis, the data were obtained either by personal contact with the authors or derived from the published data where available.
MATERIALS AND METHODS

Literature search
An exhaustive search was undertaken to identify all clinical studies that compared the microbiological status of pre-medicated and post-medicated human root canals. The MEDLINE database was searched via the EviDents search engine (http://medinformatics.uthscsa.edu/EviDents/ last accessed 20th December 2005) using CALCIUM HYDROXIDE and BACTERIA as keywords, which automatically created a complex search strategy (Table 7.1). 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 (Alderson et al. 2004). The search of the MEDLINE database included all years from 1966 to December 2005. A similar search was undertaken on EMBASE (1988 to 2005). 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. One hundred and fifty four studies were subjected to the preliminary analysis. Titles and abstracts, where available, were scanned and the relevance of each study to the antibacterial efficacy of calcium hydroxide 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. One hundred and forty-three studies were
excluded from the list, and the eleven remaining articles were subjected to stricter exclusion criteria.

**Inclusion and exclusion**

The full texts of the remaining papers were then obtained and reviewed, and the inclusion criteria (Table 7.2) were applied. Reference lists from identified articles were scanned to identify other potentially relevant preceding articles (a backward search) (three more articles were identified: (Safavi et al. 1985, Reit & Dahlén 1988, Sundqvist et al. 1998). 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) (two more articles were identified: Waltimo et al. 2005, McGurkin-Smith et al. 2005).

**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. Authors of three studies were contacted to acquire additional information not available in the published article namely, the number of teeth with negative cultures at S2 that were positive at S3, i.e. culture reversal.

**Meta-Analysis**

Between-study heterogeneity was assessed using the standard $\chi^2$ test or Q statistic. The principal measure of treatment effect (antibacterial efficacy) was risk difference, which is normally defined as the risk in the experimental group
minus risk in the control group. For the purpose of this study it is given as the
difference in the proportion of bacterial positive cultures between pre- and post-
medication (S2 vs S3). Risk difference is a measure of the impact of the
treatment on the number of events (the number of positive cultures), since it
takes into account the prevalence of the event, i.e. how common it is (Sutton 2000).
Risk differences of included studies were combined as generic inverse
variance data type (RevMan Version 4.2.7, The Cochrane Collaboration's
December 2005), taking into account the separate tracking of positive and
negative cultures at S2. The random effects model for combining study
estimates was used and an overall estimate was produced (Sutton 2000). The
level of statistical significance was set at 0.05.

RESULTS

Included and excluded studies

Eight studies met the inclusion criteria (Table 7.2): (Ørstavik et al. 1991, Sjögren
studies that compared microbiological status of pre-medicated and post-
medicated human root canals were excluded for various reasons (Table 7.3).

Only one study included a small control group (12 teeth), in which canals were
left empty (no intracanal medicament) between appointments (Waltimo et al.
2005). The remaining seven studies simply compared the frequency of positive
cultures before and after calcium hydroxide medication.
Data summary of included studies
Sample size ranged from 18 to 60 teeth. None of the papers reported the rationale for selecting the sample size. Endodontic treatment procedures varied among studies in type of instrumentation technique, concentration of sodium hypochlorite used as irrigant, removal of smear layer, and the method and duration of placement of calcium hydroxide. Overall, the clinical procedures followed accepted standards, with the following exceptions: 1) Ørstavik et al. (1991) used saline rather than sodium hypochlorite as irrigant, thus omitting a major component of antibacterial action during canal debridement; 2) Yared & Bou Dagher (1994) undertook minimal canal enlargement, such that all canals still had positive culture at S2; 3) Only one study (McGurkin-Smith et al. 2005) reported removing the smear layer using EDTA; 4) Peters et al. (2002) did not use a lentulo spiral to place calcium hydroxide in the canals. Sodium hypochlorite was used as an irrigant with concentration ranging between 0.5-5.25%. However, effects of different NaOCl concentrations on microbiological status have not been demonstrated clinically. Calcium hydroxide was used over different durations (1-4 wks). Again, the duration of calcium hydroxide dressing seems to be inconsequential once a 1-week duration is reached (Sjögren et al. 1991).

Microbiological technique
Most of the studies followed strict protocols for pre-sample sterilization of the tooth surface (Möller 1966), although some of the studies deviated slightly from this. This deviation seemed, however, unimportant because all studies reported 0% or close to 0% positive cultures of pre-sample sterilization (control sample),
i.e. sterilization protocols of the tooth surface before canal access were adequately effective. Exact procedures of the initial bacterial sample prior to canal preparation (S1) varied from study to study, but S1 results showed 100% or close to 100% bacterial positive cultures in all studies. Canal preparation protocols were widely diverse, ranging from small master apical sizes (which in practical terms equates to minimal canal debridement) to unusually large master apical size. Pre-medication sample (S2) protocols also varied from simple (charcoal paper points used to absorb canal contents) to complex. Reflecting this variability, S2 results ranged from 14.3% to 100% positive bacterial cultures. Post-medication sample (S3) protocols were similar in all studies. Citric acid was generally used to neutralize calcium hydroxide and sampling techniques were repeated as in S2. S3 results ranged from 0% to 71.4% positive to bacterial culture.

**Meta-analysis**

Outcomes of individual studies and a summary of meta-analysis results are shown in Table 7.3, Table 7.4, Table 7.5 and Figure 7.1. Six studies demonstrated a statistically significant reduction in the number of bacteria-positive canals after medication, whilst two did not. Meta-analysis was performed on the combined data. The outcome measure was based on binary data, i.e. positive/negative bacterial cultures. A comparison was made between pre- and post-medication of the same root canals (matched samples or matched pair designs). Thus, McNemar's test, which could take culture reversal into consideration by separately tracking canals with positive and negative cultures at S2, was performed on outcome measures (Moore & McCabe 2003). This test
provided a significance level (P-value) for individual studies as shown in Table 7.6. Between-study heterogeneity was assessed using the standard $\chi^2$ test or Q statistic. The eight studies were heterogeneous (Test of Homogeneity Cochran Q (ChiSq)=111.93 df=7 p<0.001). Thus, random effect methods for combining study estimates were used and an overall estimate was produced. Risk differences of included studies were combined as generic inverse variance data type ($RD_{Pooled} = -21\%; 95\% CI: -47\% \text{ to } 6\%$). The difference between pre-medication and post-medication was not statistically significant (p=0.12). Thus, based on the current best available evidence, calcium hydroxide has limited efficacy in eliminating bacteria from human root canal when assessed by the culture technique.

**DISCUSSION**

**The level of evidence**

Randomized-controlled clinical trials are high in the hierarchy of quality of evidence for determining therapeutic efficacy. These trials can establish the most convincing causal relationship (Greenhalgh 2006) because they minimize confounders and maximize control over the trial environment (Elwood 1998). Even though seven of the eight included studies in this review were not randomized-controlled trials, the fact that the same roots were sampled before and after medication made them self-controlled (identical subjects for pre- and post-medicated samples) and the results provided were more efficient statistically because of the increased inference power. The eighth study (Waltimo et al. 2005) was a randomized prospective controlled trial that
included a group of non-medicated canals, but the numbers in each group were small and the data were part of a larger study (Trope et al. 1999), in which microbiological data were not described. Waltimo et al. (2005) did not report a significant benefit for calcium hydroxide medication compared with empty canals (Chi square test with Yates correction; p=0.31).

**Publication bias**

Publication bias is a tendency that some studies are less likely to be published if studies show non-statistically significant results or if the results go against the prevailing theory. Publication bias could falsely skew the conclusion of meta-analyses in either direction. Funnel plots and rank correlation tests can determine if publication bias exists (Begg & Mazumdar 1994, Sutton 2000), however, at least 25 studies are required for these tests to be informative (Glasziou 2001). Therefore, the existence of publication bias can neither be confirmed nor denied in this review.

**Heterogeneity**

*a. Subject differences*

Patients from different geographical and ethnic backgrounds could have different composition of their oral microbial flora. This could be the result of either ethnic difference *per se* or related environment or even diet. Whatever the true cause of these differences, it has been shown that such differences in microbial flora do exist (Umeda et al. 1998, Baumgartner et al. 2004). Patients of included studies were drawn from the United States, Sweden, the Netherlands and Lebanon. This geographical difference could potentially result
in differences of endodontic microbial milieu and hence susceptibility to calcium hydroxide.

b. Canal preparation protocol differences
Canal preparation protocols were diverse among the eight studies though generally within accepted clinical procedures. In one study, only maxillary central incisors were utilized (Yared & Bou Dagher 1994). They were prepared to only size 30 or 40; theoretically, many canals were likely to be inadequately enlarged. This may be the reason why post-canal preparation sample (pre-medicated sample or S2) was 100% positive to bacterial culture, which could spuriously inflate antibacterial efficacy of calcium hydroxide in comparison to other studies, where S2 was much lower than 100%.

c. Method of calcium hydroxide placement
A lentulo spiral was used to place calcium hydroxide in all but one study, in which calcium hydroxide was carried and plugged with the blunt end of a paper point (Peters et al. 2002). This method of placement has been shown in extracted teeth to be inferior to the lentulo spiral method, in terms of increasing the pH in dentine (Teixeira et al. 2005). The latter authors conjectured that the paper point placement method was unable to fill an entire canal, resulting in a lower pH value and reduced antibacterial efficacy. The study of Peters et al. (2002) was mainly responsible for the heterogeneity among the eight studies, and had it been excluded, meta-analysis would have shown a significant effect of calcium hydroxide (Fig 2). Exclusion was, however, not justified because the
paper clearly stated that the completeness of placement of calcium hydroxide was confirmed radiographically.

**d. Outliers**

Outliers are observations that for some reason do not fit within the typical range of others. They can cause potential computational and inference problems, which could lead to distortion of estimates and P-value resulting in faulty conclusions. However, ignoring outliers or simply discarding them at will is not a good scientific approach (Barnett & Lewis 1994). Only as a last resort should outliers be deleted, if legitimate errors can be identified. In a general sense, Peters et al. (2002) and Waltimo et al. (2005) were outliers (Fig 1), however, no methodological errors or biological reasons could be identified; as a result exclusion of these was not justifiable. In addition, these two articles were not statistically considered outliers as such. To determine whether any particular data set is an outlier, the inter-quartile-range (IQR) needs to be calculated. IQR is a range between first and third quartile. Any data set that lies in between third quartile + 1.5 IQR and first quartile – 1.5 IQR is not considered an outlier (Barnett & Lewis 1994). The data from Peters et al. (2002) and Waltimo et al. (2005) were within this range.

**Diagnostic accuracy of the microbiologic sampling technique**

Microbiological sampling of root canals is complex and its accuracy has been questioned (Molander et al. 1990). It has been hypothesized that this inaccuracy could stem from the anatomical complexity of the root canal system. Bacteria reside within dentinal tubules and in accessory canals, fins and other
irregularities preventing bacteria from being easily retrieved by microbiologic sampling. Additionally, remnants of antibacterial medication may enter the sample, suppress growth at the laboratory and bring about a false negative result (Reit et al. 1999). Calcium hydroxide by itself has been shown to compromise the sensitivity of microbiological sampling (Molander et al. 1990). Sensitivity was only 33% when canals had been dressed with calcium hydroxide.

The present review has substantiated this view by clearly documenting culture reversals in four of the eight studies (Table 7.5). Thus, negative culture clearly does not equate to elimination of bacteria from the entire root canal system, which raises questions of the value of current microbiological sampling techniques (Wu et al. 2006).

Analysis of colony forming unit counts (CFU) would be useful additional information rather than positive or negative cultures as reported here; however, only four papers reported CFU, and then only either mean or median CFU. Unless the individual patient data are available, no detailed analysis is possible.

**CONCLUSION**

Based on the current best available evidence, calcium hydroxide has limited effectiveness in eliminating bacteria from human root canals when assessed by culture technique. The quest for better antibacterial protocols and sampling techniques must continue to ensure that bacteria have been reliably eradicated prior to obturation.
Table 7.1 Search strategy automatically formulated by EviDents search engine to find studies that compared microbiological status of pre-medicated and post-medicated human root canals.

<table>
<thead>
<tr>
<th>No.</th>
<th>Search history</th>
<th>Results</th>
</tr>
</thead>
</table>
Table 7.2 Inclusion and exclusion criteria used in the analysis

<table>
<thead>
<tr>
<th>Inclusion criteria</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Subjects had a non-contributory medical history;</td>
<td></td>
</tr>
<tr>
<td>2. Subjects presented with mature teeth and radiographic evidence of periapical bone loss (as an indication of pre-operative canal infection);</td>
<td></td>
</tr>
<tr>
<td>3. All selected root canals had not received any endodontic treatment previously;</td>
<td></td>
</tr>
<tr>
<td>4. Subjects underwent non-surgical root canal treatment during the study;</td>
<td></td>
</tr>
<tr>
<td>5. Teeth were dressed with calcium hydroxide sealed in the canals;</td>
<td></td>
</tr>
<tr>
<td>6. Microbiological sampling was undertaken during the course of treatment, before canal preparation (S1), after canal preparation (S2), and after canal medication (S3);</td>
<td></td>
</tr>
<tr>
<td>7. Aerobic and anaerobic culturing techniques were performed on all samples;</td>
<td></td>
</tr>
<tr>
<td>8. Treatment outcome was stated in terms of positive and negative canal cultures.</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Exclusion criteria</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Inclusion of test teeth without infected necrotic root canal systems and/or radiographic evidence of periapical bone loss (hence no preoperative canal infection);</td>
<td></td>
</tr>
<tr>
<td>2. Study carried out on failed, endodontically treated teeth (retreatment cases);</td>
<td></td>
</tr>
<tr>
<td>3. No post-instrumentation sample (S2);</td>
<td></td>
</tr>
<tr>
<td>4. Post-medication sample (S3) not taken immediately after removal of the test medicament;</td>
<td></td>
</tr>
<tr>
<td>5. Use of multiple antibacterial medicaments in succession, in the same canal;</td>
<td></td>
</tr>
<tr>
<td>6. Repeated cleaning and irrigation procedures in multiple appointments;</td>
<td></td>
</tr>
<tr>
<td>Excluded studies</td>
<td>Reason for exclusion</td>
</tr>
<tr>
<td>----------------------------------------</td>
<td>----------------------</td>
</tr>
<tr>
<td>Cvek et al. 1976 (Cvek et al. 1976)</td>
<td>1</td>
</tr>
<tr>
<td>Byström et al. 1985</td>
<td>3</td>
</tr>
<tr>
<td>Safavi et al. 1985</td>
<td>1, 6</td>
</tr>
<tr>
<td>Reit &amp; Dahlén 1988</td>
<td>3</td>
</tr>
<tr>
<td>Barbosa et al. 1997 (Barbosa et al. 1997)</td>
<td>4</td>
</tr>
<tr>
<td>Sundqvist et al. 1998</td>
<td>2, 3</td>
</tr>
<tr>
<td>Molander et al. 1999 (Molander et al. 1999)</td>
<td>4, 5</td>
</tr>
<tr>
<td>Peciuliene et al. 2001 (Peciuliene et al. 2001)</td>
<td>2</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Included studies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ørstavik et al. 1991</td>
</tr>
<tr>
<td>Sjögren et al. 1991</td>
</tr>
<tr>
<td>Yared &amp; Bou Dagher 1994</td>
</tr>
<tr>
<td>Shuping et al. 2000</td>
</tr>
<tr>
<td>Peters et al. 2002</td>
</tr>
<tr>
<td>Kvist et al. 2004</td>
</tr>
<tr>
<td>McGurkin-Smith et al. 2005</td>
</tr>
<tr>
<td>Waltimo et al. 2005</td>
</tr>
</tbody>
</table>
Table 7.4 Data summary of included studies showing the number of bacteria-positive canals at each sampling point.

<table>
<thead>
<tr>
<th>Citation</th>
<th>Sample size</th>
<th>S1 (%)</th>
<th>S2 (%)</th>
<th>S3 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ørstavik et al. 1991</td>
<td>23</td>
<td>22 (95.7)</td>
<td>13 (56.5)</td>
<td>8 (34.8)</td>
</tr>
<tr>
<td>Sjögren et al. 1991</td>
<td>18</td>
<td>18 (100)</td>
<td>9 (50)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Yared &amp; Bou Dagher 1994</td>
<td>60</td>
<td>60 (100)</td>
<td>60 (100)</td>
<td>19 (31.7)</td>
</tr>
<tr>
<td>Shuping et al. 2000</td>
<td>40</td>
<td>39-40 (97.5-100)</td>
<td>14-16 (35-40)</td>
<td>3 (7.5)</td>
</tr>
<tr>
<td>Peters et al. 2002</td>
<td>21</td>
<td>21 (100)</td>
<td>3 (14.3)</td>
<td>15 (71.4)</td>
</tr>
<tr>
<td>Kvist et al. 2004</td>
<td>44</td>
<td>43 (95.5)</td>
<td>28 (63.6)</td>
<td>16 (36.4)</td>
</tr>
<tr>
<td>McGurkin-Smith et al. 2005</td>
<td>27</td>
<td>25 (92.6)</td>
<td>14 (51.9)</td>
<td>5 (18.5)</td>
</tr>
<tr>
<td>Waltimo et al. 2005</td>
<td>18</td>
<td>18 (100)</td>
<td>4 (22.2)</td>
<td>6 (33.3)</td>
</tr>
</tbody>
</table>

S1=bacterial sampling after initial access

S2=bacterial sampling after the cleaning and shaping procedure is complete (immediately before canal medication)

S3=bacterial sampling when the canal is re-accessed 1-4 weeks later, after the medication has been removed

* Exact data were not available after repeated attempts to contact authors.
<table>
<thead>
<tr>
<th>Citation</th>
<th>Sample size</th>
<th>$S_{2^+} \rightarrow S_{3^+}$</th>
<th>$S_{2^-} \rightarrow S_{3^+}$</th>
<th>$S_{2^+} \rightarrow S_{3^-}$</th>
<th>$S_{2^-} \rightarrow S_{3^-}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ørstadik et al. 1991</td>
<td>23</td>
<td>8</td>
<td>0</td>
<td>5</td>
<td>10</td>
</tr>
<tr>
<td>Sjögren et al. 1991</td>
<td>18</td>
<td>0</td>
<td>0</td>
<td>9</td>
<td>9</td>
</tr>
<tr>
<td>Yared &amp; Bou Dagher 1994</td>
<td>60</td>
<td>19</td>
<td>0</td>
<td>41</td>
<td>0</td>
</tr>
<tr>
<td>Shuping et al. 2000</td>
<td>40</td>
<td>3</td>
<td>0</td>
<td>11-13*</td>
<td>24-26*</td>
</tr>
<tr>
<td>Peters et al. 2002</td>
<td>21</td>
<td>3</td>
<td>12</td>
<td>0</td>
<td>6</td>
</tr>
<tr>
<td>Kvist et al. 2004</td>
<td>44</td>
<td>11</td>
<td>5</td>
<td>17</td>
<td>11</td>
</tr>
<tr>
<td>McGurkin-Smith et al. 2005</td>
<td>27</td>
<td>3</td>
<td>2</td>
<td>11</td>
<td>11</td>
</tr>
<tr>
<td>Waltimo et al. 2005</td>
<td>18</td>
<td>0</td>
<td>6</td>
<td>4</td>
<td>8</td>
</tr>
</tbody>
</table>

* Exact data were not available after repeated attempts to contact authors.
Table 7.6 Meta-analysis data summary of included studies (Minus value indicates that calcium hydroxide medication reduced the number of positive cultures.)

<table>
<thead>
<tr>
<th>Citation</th>
<th>Sample size</th>
<th>Rate difference (%)</th>
<th>95% CI</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ørstavik et al. 1991</td>
<td>23</td>
<td>-22</td>
<td>-40 -4</td>
<td>0.04</td>
</tr>
<tr>
<td>Sjögren et al. 1991</td>
<td>18</td>
<td>-50</td>
<td>-74 -26</td>
<td>0.008</td>
</tr>
<tr>
<td>Yared &amp; Boudagher 1994</td>
<td>60</td>
<td>-68</td>
<td>-80 -56</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Shuping et al. 2000</td>
<td>40</td>
<td>-28</td>
<td>-42 -14</td>
<td>0.003-0.001*</td>
</tr>
<tr>
<td>Peters et al. 2002</td>
<td>21</td>
<td>57</td>
<td>35 79</td>
<td>0.002</td>
</tr>
<tr>
<td>Kvist et al. 2004</td>
<td>44</td>
<td>-27</td>
<td>-47 -7</td>
<td>0.019</td>
</tr>
<tr>
<td>McGurkin-Smith et al. 2005</td>
<td>27</td>
<td>-33</td>
<td>-57 -9</td>
<td>0.027</td>
</tr>
<tr>
<td>Waltimo et al. 2005</td>
<td>18</td>
<td>11</td>
<td>-22 44</td>
<td>0.752</td>
</tr>
<tr>
<td>Combined 8 studies</td>
<td>251</td>
<td>-21</td>
<td>-47 6</td>
<td>0.12</td>
</tr>
</tbody>
</table>

* Exact data were not available after repeated attempts to contact authors.
Figure 7.1 Forest plot

- **Review:** Antibacterial efficacy of calcium hydroxide
- **Comparison:** Oral premedication vs Post-medication
- **Outcome:** 11 studies by general inverse variance

<table>
<thead>
<tr>
<th>Study Sub-category</th>
<th>With Calcium N</th>
<th>Without Calcium N</th>
<th>Rate Difference (SE)</th>
<th>95% CI</th>
<th>Rate difference (random)</th>
<th>Weight %</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>1991 Oravsky</td>
<td>23</td>
<td>23</td>
<td>-0.2260 (0.0930)</td>
<td></td>
<td></td>
<td>12.82</td>
<td>-0.493, -0.04</td>
</tr>
<tr>
<td>1994 Sugren</td>
<td>18</td>
<td>18</td>
<td>-0.5060 (0.1230)</td>
<td></td>
<td></td>
<td>12.27</td>
<td>-0.744, -0.28</td>
</tr>
<tr>
<td>1995 Yared</td>
<td>60</td>
<td>60</td>
<td>-0.5660 (0.0500)</td>
<td></td>
<td></td>
<td>13.24</td>
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</tr>
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<td>40</td>
<td>40</td>
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<td></td>
<td></td>
<td>19.12</td>
<td>-0.365, 0.14</td>
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<tr>
<td>2003 Petras</td>
<td>21</td>
<td>21</td>
<td>-0.3760 (0.1330)</td>
<td></td>
<td></td>
<td>12.46</td>
<td>-0.573, 0.29</td>
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<tr>
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<td>44</td>
<td>-0.2760 (0.1090)</td>
<td></td>
<td></td>
<td>12.45</td>
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<td>2005 McFool-Smith</td>
<td>27</td>
<td>27</td>
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<td></td>
<td></td>
<td>12.27</td>
<td>-0.344, -0.05</td>
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<tr>
<td>2008 Palme</td>
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<td>10</td>
<td>0.1180 (0.1700)</td>
<td></td>
<td></td>
<td>11.17</td>
<td>-0.622, 0.48</td>
</tr>
</tbody>
</table>

Total (95% CI): 251 251
Test for heterogeneity: Chi² = 111.83, df = 7 (p = 0.0001), I² = 93.7%
Test for overall effect: Z = 1.856 (p = 0.033)

Horizontal line in Forest plot shows the 95% confidence interval; the shorter the line, the higher the precision of the study.

Negative and positive value of risk difference is used to indicate the differences in direction of the value.

Black boxes indicate the mean risk difference; their sizes are proportional to their sample size.

The black diamond is the pooled result, with horizontal tips indicating 95% confidence interval, and the vertical tips indicating pooled risk difference.

The vertical line at zero indicates no difference in percentage of the number of positive cultures between pre- and post-medication.
REFERENCES:


8 A CONFLICT IN DECISION-MAKING PHILOSOPHY: CRITICAL APPRAISAL OF MICROBIOLOGICAL ROOT CANAL SAMPLING

How useful is root canal culturing in predicting treatment outcome?

A manuscript published in


**RESEARCH QUESTION:**

How useful is root canal culturing in predicting treatment outcome?
ABSTRACT

Microbial control is fundamental to healing of apical periodontitis, and is central to endodontic practice. The effectiveness of antibacterial measures is generally monitored (in clinical research studies) by microbiological root canal sampling (MRS), which is often used as a predictor for healing. This article addresses the question of the extent to which positive or negative cultures at time of obturation are able to predict treatment outcome. To date only one small clinical study has attempted to relate the treatment outcome to intraradicular bacterial status (p=0.025, Fisher’s exact test): the strength of the association was not great, with a wide confidence interval (odds ratio=7.2; 95%CI: 1.5 to 34.2). The extent to which current canal sampling techniques accurately reflect the bacterial status of the canal space must also be taken into account. False positive and negative cultures may adversely affect the performance of MRS. These conditions emphasize how potentially error-prone MRS can be. As currently practised, intracanal sampling techniques suffer from deficiencies that limit their predictive value. This article in no way questions the role of intracanal bacteria in causing apical periodontitis, nor the central role of bacterial control in endodontic treatment. Rather, it emphasizes the need for more detailed clinical studies of bacterial status and healing, as well as refinement of techniques for microbial sampling of canals.
INTRODUCTION

It has been well established that apical periodontitis is caused by bacteria within the canal space (1, 2). The treatment of apical periodontitis should, therefore, be removal of the cause i.e. bacterial eradication. As a result, current treatment protocols (isolation, canal preparation, antibacterial irrigants and intracanal medicaments) are directed towards bacterial elimination. Because of this intimate involvement of bacteria and clinical endodontics, the rationales for, and development of, treatment protocols are all based on data involving microbiological root canal sampling (MRS) (3-8). In other words, MRS is the very foundation of clinical endodontics.

MRS results have been used widely in clinical endodontic research as a predictor (a surrogate endpoint) for clinical outcomes (healing). A surrogate endpoint is a variable which is relatively easily measured and which predicts a distant outcome of a therapeutic intervention, but which is not in itself a direct measure of clinical benefit (9). A major important feature of surrogate endpoints is that they can considerably reduce the sample size, duration, cost and, therefore, difficulties of clinical studies. Its shortcoming, however, is that the surrogate endpoint may not closely reflect the treatment target; in other words it may not be sensitive enough to predict treatment outcome effectively.

In this article we address the question of the extent to which positive or negative cultures at the time of obturation adequately predict treatment outcome, i.e. healing of apical periodontitis.
MRS entails several technique-sensitive steps (10). It is a complicated procedure performed in an extremely challenging environment. The oral cavity is naturally full of bacteria, which can easily contaminate a sample. Based on Möller’s work (10), to perform MRS properly several steps must be followed: firstly, the operative field needs to be prepared by scaling of hard and soft deposits and be effectively isolated with rubber dam. Secondly, the operative field is sterilized with 30% hydrogen peroxide followed by 5% tincture of iodine. Thirdly, sterility of the operative field is monitored by sampling tooth surfaces with a charcoal-impregnated pellet. This pellet will be cultured and if it is positive to bacteria, any microbiological data obtained from that particular tooth must be discarded because of the risk of contamination. Fourthly, the root canal is filled with sampling fluid; a sample is taken with charcoal-impregnated points that are transferred to a transport medium. Fifthly, the medium is then serially diluted and inoculated into an appropriate nutrient broth and/or agar plates. These are aerobically and anaerobically incubated for a period of time long enough to allow even slowly growing species to form colonies. Lastly, results are microbiologically analyzed using growth-no growth determination or identification of isolated microorganisms based on colony morphology, micromorphology, physical and biochemical tests (11).

MRS is, basically, a passive sample of the main root canal space, which does not include inaccessible areas such as accessory canals, fins and dentinal tubules nor adherent biofilms. Anaerobic sampling and cultivation techniques are indispensable to analyses of MRS and they are far from straightforward. A
special medium supplemented with agar is generally required to prevent oxygen diffusion so that toxic intermediates of oxygen do not accumulate and interfere with viability of anaerobic bacteria (12). Moreover, to obtain growth from potentially positive samples, the incubation time must not be less than about two weeks, which, from a microbiological research perspective, is costly and time-consuming (10).

Culture-based identification methods are often unable to reproduce growth conditions required by fastidious bacteria that have stringent environmental and nutritional requirements. In this respect, many bacterial species are difficult or impossible to culture, and evidence is now emerging that there are species involved in endodontic infections that are uncultivable (13, 14). Because of the limitations of culture-based identification methods, a relatively new technique in microbiology has been developed to identify microorganisms without culturing. Molecular-based identification methods (PCR) are designed to detect microbial DNA rather than living microorganisms. A limitation of PCR is that it cannot distinguish between DNA from viable or dead cells, and it is therefore unclear whether the results from this method truly represent the authentic living endodontic flora, or rather a historical record of organisms that have entered but not survived in the root canal (15). It is important to realize that clinical samples for PCR analysis are acquired by the same method as for culturing (i.e. soaking up sampling fluid from the root canal with paper points), and are therefore equally susceptible to contamination and to false positive and/or negative results.
The focus of this review is, however, on MRS and culture-based identification methods, because molecular-based methods are still under continuous improvement and long-term endodontic clinical outcome studies using molecular methods are unavailable at this stage.

**Data reported from MRS**

Some studies report MRS results as bacterial counts and/or bacterial species; however, the clinical significance of all bacteria in endodontics is not fully known. Hence, a link between bacterial load/bacterial species and clinical outcomes has never been firmly established. The majority of the endodontic studies that measure therapeutic efficacy of medicaments or other treatment protocols have reported MRS results simply as positive or negative cultures (3-8). Positive or negative culture results have been related to clinical outcomes (healing), either by correlation within the same study (16) or interpreted as a predictor for healing (6-8). The effect of intraradicular bacterial status on treatment outcome has been previously investigated (17-21); however, these older studies were not considered in this review on the grounds that inadequate microbiological techniques were used (no anaerobic culturing).

A complex relationship is present between MRS results and clinical outcomes. Firstly, a majority of cases (68%) healed even with a positive culture at time of obturation, although the frequency of healing was lower than in teeth with a negative culture (94%) (16). Secondly, although calcium hydroxide medication tends to reduce the number of positive cultures, this reduction does not result in a higher incidence of healing relative to root canal treated teeth without calcium hydroxide medication (22, 23). Thirdly, in culture studies of endodontically
Root canal sampling

treated teeth with and without persistent lesions, a high proportion of healed cases still had positive cultures while a high proportion of teeth with persistent lesions had negative cultures (24). Therefore, MRS results and clinical outcomes do not show a simple all-or-none relationship. Substantial numbers of canals with positive culture can heal and a number of unhealed cases yield negative cultures. Two questions arise from these observations: 1. how strong is the association between MRS results and outcome? and 2. does MRS adequately reflect the true bacterial status of the canal space?

**HOW STRONG IS THE ASSOCIATION BETWEEN MRS RESULTS (POSITIVE VS NEGATIVE CULTURES) AND CLINICAL TREATMENT OUTCOME (HEALING)?**

**Persistent disease and culture studies in initial treatment**

Essentially 100% of teeth with periapical lesions have positive cultures before treatment begins (22, 25, 26). There is no question of the relationship between intracanal bacteria and periapical disease (1, 2). However, when looking at treatment related issues, and specifically the results of MRS and clinical healing, a more complex picture emerges. No significant difference exists in outcomes for single- and multiple-visit endodontics (23). The clinical difference between single- and multiple-visit endodontics is that root canals are medicated with calcium hydroxide (or other intracanal medicaments) in multiple-visit endodontics. Calcium hydroxide intracanal dressing has been associated with enhanced bacterial elimination, as demonstrated by a reduction in the number of positive root canal cultures (22). Consequently, multiple-visit endodontics
should have a higher chance of achieving negative culture status before obturation. However, this higher chance does not equate to higher healing rates, as documented by three randomized controlled clinical trials (27-29) and a meta-analysis of such trials (23).

Only one study with an acceptable microbiological sampling technique has directly associated the clinical outcome (healing) of teeth with positive vs negative cultures at the time of obturation (16). In this study of 53 single rooted teeth, all canals were prepared and obturated in a single visit (no intracanal medication used). Culture status was determined from post-instrumentation samples taken from each canal. All samples were meticulously processed under strict anaerobic techniques. Twenty-two cases yielded positive cultures, while 31 cases were negative cultures; these cases were followed separately for healing (Table 8.1). Patients were recalled yearly for clinical and radiographic examination. Radiographs were taken using a standardized technique to obtain optimal diagnostic quality. The cases were followed for five years if complete healing had not occurred earlier. Healing was strictly determined using Strindberg’s criteria (30). Ninety four percent of canals with negative cultures healed, while 68% of canals with positive cultures healed, and culture status was significantly associated with clinical outcome (p=0.025, Fisher’s exact test).

Earlier studies that have evaluated the association of intraradicular bacterial status and treatment outcome (17-21) are of limited value because inadequate microbiological techniques were used (no anaerobic culturing). These studies reported small differences in outcome of 10 to 15%. A recent article reported a similar conclusion to Sjögren et al. (16), i.e. negative cultures were significantly
associated (p<0.01) with successful clinical outcomes (31). In this study of 30 cases, however, bacterial status prior to completion of cleaning and shaping procedures was used to calculate this association rather than sampling immediately before obturation. Therefore, the results were not indicative of final bacterial status prior to obturation and cannot be interpreted in the same fashion as Sjögren et al. (16).

Considering bacterial status prior to obturation as a risk factor for disease (in this case persistent apical periodontitis), the concept of risk difference and odds ratio can be utilized, and analysis of the study of Sjögren et al. (16) can be carried one step further by quantifying the strength of the association.

Risk difference is defined as the risk in the experimental group minus risk in the control group. For the purpose of this study it is given as the difference in healing rates between teeth with negative and positive cultures. Risk difference is a measure of the impact of the treatment on the number of events (healing), since it takes into account the prevalence of the event, i.e. how common it is. This is in contrast to the odds ratio, which is a measure of the association between treatment and outcome, but does not give an indication of the impact of the intervention, i.e. the same odds ratio can give a different impact depending on how common the event is (32).

Teeth with negative cultures had a reduced risk of persistent disease of 25.4 percentage points (risk difference=25.4%; 95%CI: 4.6% to 36.3%) (33). The odds for apical lesion of teeth with negative cultures to heal completely after treatment are 6.8 times that of teeth with positive cultures (odds ratio=6.8;
95%CI: 1.4 to 32). An odds ratio of this magnitude may seem to be a very strong association; however, from an epidemiological viewpoint this number may not be particularly high (34). Relatively, intraradicular bacterial status may not be as strong a predictor of clinical outcomes as historically perceived. In addition, the wide confidence interval of risk difference (4.6% to 36.3%) and odds ratio (1.4 to 32) reflects a low precision of the study, i.e. there is a 95% chance that a true value of risk difference in a population could be anywhere between 4.6% and 36.3%, and the true odds ratio could be any value between 1.4 (almost no association) to 32 (strong association).

Relying on one small study as the basis for treatment recommendations is not very prudent. A useful analogy is the series of clinical studies comparing the effects of quality of obturation and restoration (apical vs coronal seal) on healing. In the first such study Ray and Trope (35) concluded that the quality of coronal restoration was significantly more important than the quality of endodontic filling to treatment outcome (p<0.001, Chi square test) (odds ratio=2.6; 95%CI; 1.8 to 3.9). However, a succeeding article (36) reported the completely opposite result. When five studies investigating the same issue (35-39) were identified and were statistically combined, a different picture emerged. The highly significant result in Ray and Trope (35) became non-significant (p=0.55) with odds ratio of 0.8 (95%CI; 0.3 to 1.8) (meta-analysis data using random effect method, RevMan Version 4.2.7). This emphasizes the point that one study is not sufficient, and that clinical confirmation is needed.

If intraradicular bacterial status at the time of obturation were the only factor influencing clinical outcomes, bacterial status should be a perfect outcome
predictor. However, the idea of “single factor produces single effect” is probably too simplistic and does not fit the complex relationship between host and disease. The host response and/or quality of coronal restoration could also influence endodontic clinical outcomes (35-40). It is unrealistic to expect that a culture taken at a single time point immediately before obturation will be a perfect predictor of outcome.

**Persistent disease and culture studies in endodontically treated teeth**

MRS has revealed that 32-56% of endodontically treated teeth with persistent apical lesions (failed cases) were negative to bacterial cultures (24, 41). Causes other than intraradicular infections may be responsible for persistent lesions e.g. true cyst, extraradicular infection, foreign body reaction, scar tissue (42), which cannot be managed by orthograde endodontic treatment. However, given the high healing incidence (more than 90%) of orthograde endodontic treatment (43), causes of persistent lesions other than intraradicular infections should not account for more than 10% of cases. Taking this into consideration, the percentage of failed cases negative to bacterial cultures is rather higher than might be predicted (24, 41).

Only one study has directly compared the culture status of endodontically treated teeth with and without persistent apical lesions (24). In that study, 100 teeth with persistent lesions were cultured after removal of the root canal filling, and compared with 20 teeth without a lesion (retreated for restorative reasons). All teeth had been root treated at least four years before the commencement of retreatment to ensure that all apical lesions can be considered “failure” (30). An
anaerobic sampling technique as laid out by Möller (10) was strictly followed. In 99 cases, root filling material was successfully removed only by mechanical means to make certain that the bacterial milieu was minimally disrupted. However, in 21 cases chloroform was required to soften the gutta percha. The study showed that 45% of ‘healed’ teeth had positive cultures, and 32% of ‘diseased’ teeth showed negative culture. A subsequent study using molecular techniques has also substantiated that residual bacteria can be detected in a high proportion (77%) even of successful cases (44).

Even though this result is counter-intuitive, the raw data from Molander et al. (24) (Table 8.2) show that the results of MRS in endodontically treated teeth have no significant association with clinical outcomes (P value=0.09, Chi square test with Yates correction; OR=2.6 95%CI: 1 to 6.8). However, calculations were based on only a small number of endodontically treated teeth without lesions (n=20). Moreover, the sample size of the two groups in the comparison was markedly different (100 vs 20) making statistics less efficient; the inference power was lower as a result. Lastly, the study was cross-sectional in design, which has a limited ability to indicate a causal relationship.

In summary, the association between MRS results and healing is based solely on one small study (n=53), resulting in a wide confidence interval for risk difference and odds ratio (16). More clinical studies are needed. A relatively high proportion of failed cases are found to have negative cultures and a high proportion of successful cases to have positive cultures. This evidence strongly suggests that root canal bacterial status as determined by MRS and culturing has limited value in predicting clinical success (healing). Given the
unquestioned relationship between intracanal bacteria and apical periodontitis (1, 2, 25) and the low frequency of non-bacterial factors in persistent disease (42), the question then arises: to what extent do current canal sampling techniques accurately reflect the bacterial status of the canal space?

**DOES MRS RESULT ADEQUATELY REFLECT THE TRUE BACTERIAL STATUS OF THE CANAL SPACE?**

**Theoretical framework**

To determine if a test measures what it claims, the “truth” or “gold standard” needs to be known, against which test results are compared. Two by two tables can then be constructed (Table 8.3). Five measures can be derived from this table and used to evaluate the test (Table 8.4). Sensitivity and specificity tell about the test in general, whereas the predictive value tells about what a particular test results means for the particular tooth/canal. For that reason sensitivity and specificity are more appropriate than others to measure performance of the test.

**Performance of microbiological root canal sampling**

In terms of evaluating the accuracy of root canal sampling, the truth is not known unless all tested teeth can be assessed by an independent measurement that is known to be reliable (the “gold standard”). One article directly demonstrated that negative root canal cultures did not necessarily indicate sterility of the root canal (45). In this study, 20 infected human teeth were extracted. The outer tooth surface was sterilized by means of ultraviolet light.
Sterilization of the outer tooth surface was controlled and examined by streaking on agar plates. If sterilization was not successful, data from that particular tooth were discarded. Canals were then accessed and prepared extraorally. Root canal samples were taken using paper points and were cultured aerobically and anaerobically. All teeth were finally crushed and the tooth powder was cultured. Viable bacteria were still found in seven teeth despite three consecutive negative cultures of MRS after complete canal preparation and medication.

It is ethically unfeasible to extract human teeth simply to establish a gold standard. To circumvent this problem, root canals can be sampled at the subsequent session after canals had been left empty or filled with nutrient broth, allowing previously irretrievable bacteria to repopulate the root canal system. This technique has been used and called “gold standard” in three articles that systematically assessed the accuracy of MRS after canal medication (46-48). The results are shown in Table 8.5.

Sample size in all three studies was relatively small, and resulted in wide confidence intervals (Table 8.5 sensitivity column) and low precision. One commonality among the three studies was that sensitivity of MRS was strongly influenced by the type of intracanal medication. Calcium hydroxide especially affected MRS sensitivity a great deal. Sensitivity was reduced to only 33% when canals had been medicated with calcium hydroxide (46). That means that a relatively high number of canals were false negative (i.e. negative cultures at initial sampling but positive at “gold standard” sampling). It seems to be a
scientific dilemma to evaluate the efficacy of intracanal medication using MRS, because the test itself can be heavily influenced by the tested materials.

These calculations depend greatly on determining false positive and false negative results, which are established from the number of culture reversals in MRS. A culture reversal is defined for the purpose of this analysis as the number of negative cultures at initial sampling, which subsequently turn positive at the “gold standard” sampling, and vice versa. In other words, the higher the number of culture reversals, the lower the accuracy of the MRS.

Culture reversal means there is a change in bacterial status between the first (test results) and second visit (gold standard) where canals have been left empty or filled with nutrient medium between visits. It has been demonstrated that bacteria can regrow in empty canals. Thirty six out of 150 canals (24%) (49) and 4 out of 12 canals (33%) (31) showed a negative culture at the first visit but were positive at the second visit seven days later when canals were left empty. On the contrary, bacteria also appear to die off in empty canals. Three of 15 canals (20%) with positive cultures at the first appointment (after canal preparation and irrigation) were negative at the next appointment two to four days later (4, 5). Regardless of the direction, culture reversal contributes substantially to inaccuracy of MRS.

**Why is performance of MRS not particularly high?**

Several possible factors play a part in culture reversal or low performance of MRS.
False negative
It is possible that bacteria may be in the root canals from the very beginning but located in inaccessible areas for MRS e.g. ramifications and dentinal tubules (50). They can repopulate root canals after the first MRS shows a negative result. In addition, a carry-over effect of antibacterial irrigants or medicaments can inhibit bacterial growth during the cultivation process provided that neutralizing procedures were not available or were not conducted properly.

False positive
MRS is a technique-sensitive procedure performed in a hostile setting. Despite every precaution being taken as Möller (10) suggested, the field of operation for endodontic procedures is not entirely sterile nor completely immune from saliva ingress and recontamination.

In addition to these false positive or negative situations, the bacterial status of the canal may actually change between appointments for “incidental” reasons unrelated to the study itself. When intraradicular bacterial status has truly changed between initial and gold standard sampling, for the purpose of this analysis, this situation is labeled “incidental”.

Incidental false negative
Bacteria may die off because of an inappropriate or nutrient-deprived root canal environment. Another possibility is that if bacteria are low in number at the initial sampling, at the second visit they might not be retrieved simply by chance. In these conditions, even though MRS has accurately detected what it is meant to detect (i.e. the actual change in bacterial status), the results will be
shown as culture reversal, which will unfavorably affect the measurement of performance of MRS. In other words, MRS has measured bacterial status correctly, but the results will be shown as incorrect and it is impossible to determine if it is actually incorrect.

**Incidental false positive**

Bacteria can reenter the root canal system between visits through coronal leakage of the temporary restoration and/or marginal deficiency (51), cracks, and exposed dentinal tubules (52). Anachoresis is possibly another potential explanation, although generally regarded as a remote possibility (53-56). Again, MRS may measure bacterial status correctly but the result will be interpreted as a reversal.

Four potential conditions which may adversely affect performance of MRS have been outlined i.e. false negative, false positive, incidental false negative, and incidental false positive. These conditions emphasize how error-prone MRS and the measurement of the performance of MRS can be.

The problem with performance of MRS appears to be one of sampling rather than the bacterial identification process. Given the possibility of biofilms and bacteria in inaccessible areas such as ramifications and dentinal tubules, passive sampling of the main canals is not likely to detect all bacteria. Ørstavik (1991) attempted to solve the problem by additional filing of the canal wall, but this will not reach inaccessible areas (57). Low-level ultrasonic agitation has been used in microbiological research to segregate clumps of bacteria without injuring the cells (58), and a similar approach could probably be applied in root
canal sampling. Its ability to dislodge bacteria from inaccessible locations especially deep within dentinal tubules is unknown.

**CONCLUSIONS**

Bacterial culturing is not an end in itself - its main purpose clinically is to serve as a predictor of healing. To date only one small study (53 cases) (16) has documented an association between culture status at the time of obturation and healing. The only study of persistent lesions and culture status of endodontically treated teeth (24) did not demonstrate a significant association. More clinical studies associating intraradicular bacterial status to healing rates are required. Culturing canals after the use of an intracanal medicament (especially calcium hydroxide) may largely demonstrate the carry-over effect of residual medicament rather than elimination of bacteria from the canal space, despite efforts to minimize the carry-over. Thus, as currently practised, intracanal sampling techniques suffer from deficiencies that limit their predictive value. This conclusion in no way questions the role of intracanal bacteria in causing apical periodontitis, nor the central role of bacterial control in endodontic treatment. Rather, it emphasizes the need for more detailed clinical studies of bacterial status and healing, as well as refinement of techniques for microbial sampling of canals.
ADDENDUM

Since the publication of this study, two more articles that studied the association of the results of MRS prior to obturation and clinical outcomes in initial treatment have been identified (29, 59). Endodontic treatment and microbiological techniques of these studies were of a high standard and on a par with the work of Sjögren et al. (16). Both studies showed no significant association of the results of MRS and clinical outcomes (p>0.05 and 0.12, respectively). In light of these two studies, the merit of MRS as a clinical outcome predictor becomes even more questionable.

A meta-analysis of the 3 studies is not possible, because Peters & Wesselink and Molander et al. (29, 59) both included an “uncertain” category, while Sjögren et al. (16) used persistent/healed only. On balance, however, there is not a statistically significant difference. Thus, the earlier (1960’s) picture has been repeated, ultimately showing that canal culturing is of little benefit in predicting outcome (healing).

The problem is most likely related to difficulties with sampling. Passive sampling will not disrupt biofilm or sample accessory canals, dentinal tubules etc. Hence regardless of whether bacteria are identified by aerobic culture (1960’s), anaerobic cultures (1970’s to present) or molecular methods, the problem will persist until sampling methods are more reliable.
Table 8.1 Raw data of Sjögren et al. (16) investigating the effect of intraradicular bacterial status (as determine by MRS and culturing) on treatment outcome in initial treatment cases.

<table>
<thead>
<tr>
<th>Sjögren et al. (16)</th>
<th>Not healed (%)</th>
<th>Healed (%)</th>
<th>totals</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive to bacteria cultures</td>
<td>7 (32%)</td>
<td>15 (68%)</td>
<td>22</td>
</tr>
<tr>
<td>Negative to bacteria cultures</td>
<td>2 (6%)</td>
<td>29 (94%)</td>
<td>31</td>
</tr>
<tr>
<td>totals</td>
<td>9</td>
<td>44</td>
<td>53</td>
</tr>
</tbody>
</table>
Table 8.2 Raw data of Molander et al. (24) investigating the effect of intraradicular bacterial status (as determined by MRS and culturing) on treatment outcome in retreatment cases.

<table>
<thead>
<tr>
<th>Molander et al. (24)</th>
<th>Not healed (%)</th>
<th>Healed (%)</th>
<th>totals</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive to bacteria cultures</td>
<td>68 (68%)</td>
<td>9 (45%)</td>
<td>77</td>
</tr>
<tr>
<td>Negative to bacteria cultures</td>
<td>32 (32%)</td>
<td>11 (55%)</td>
<td>43</td>
</tr>
<tr>
<td>totals</td>
<td>100</td>
<td>20</td>
<td>120</td>
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</tbody>
</table>
Table 8.3 Two by two table for evaluation of the test

The truth or gold standard

<table>
<thead>
<tr>
<th></th>
<th>+</th>
<th>-</th>
<th>Totals</th>
</tr>
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<tbody>
<tr>
<td>Test</td>
<td>A (true positive)</td>
<td>B (false positive)</td>
<td>A+B</td>
</tr>
<tr>
<td>results</td>
<td>C (false negative)</td>
<td>D (true negative)</td>
<td>C+D</td>
</tr>
<tr>
<td>Totals</td>
<td>A+C</td>
<td>B+D</td>
<td>A+B+C+D</td>
</tr>
</tbody>
</table>
### Table 8.4 Derived data from two by two table and their meanings

<table>
<thead>
<tr>
<th>Evaluating point</th>
<th>What does it mean? (60)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensitivity (%) $\frac{a}{a+c}$</td>
<td>How good is this test at detecting canals with bacteria present?</td>
</tr>
<tr>
<td>Specificity (%) $\frac{d}{b+d}$</td>
<td>How good is this test at correctly excluding canals without bacteria?</td>
</tr>
<tr>
<td>Positive predictive value (%) $\frac{a}{a+b}$</td>
<td>If the test is positive, what is the chance that the canal actually has bacteria present?</td>
</tr>
<tr>
<td>Negative predictive value (%) $\frac{d}{c+d}$</td>
<td>If the test is negative, what is the chance that the canal actually does not have bacteria?</td>
</tr>
<tr>
<td>Accuracy (%) $\frac{a+d}{a+b+c+d}$</td>
<td>What proportion of all tests have given the correct result?</td>
</tr>
</tbody>
</table>
Table 8.5 Summary of diagnostic accuracy of MRS

<table>
<thead>
<tr>
<th>Study</th>
<th>Medication</th>
<th>n (teeth)</th>
<th>a/a+c (95CI:% to %)</th>
<th>d/b+d (%)</th>
<th>a/a+b (%)</th>
<th>d/c+d (%)</th>
<th>a+d/a+b+c+d (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reit &amp; Dahlén 1988 (46)</td>
<td>Calcium hydroxide</td>
<td>35</td>
<td>33 (7.5 to 70)</td>
<td>81</td>
<td>38</td>
<td>78</td>
<td>69</td>
</tr>
<tr>
<td>Molander et al. 1990 (47)</td>
<td>Clindamycin</td>
<td>24</td>
<td>50 (12 to 88)</td>
<td>94</td>
<td>75</td>
<td>85</td>
<td>83</td>
</tr>
<tr>
<td>Reit et al. 1999 (48)</td>
<td>IKI</td>
<td>50</td>
<td>68 (45 to 86)</td>
<td>75</td>
<td>60</td>
<td>75</td>
<td>72</td>
</tr>
</tbody>
</table>
REFERENCES:


9 DISCUSSION
**CLINICAL FINDINGS**

The major conclusions of this study and their implications for both future research and clinical practice will be considered here. The clinically relevant findings can be summarized as follows:

1. *The effectiveness of single- and multiple-visit root canal treatment as determined by clinical and radiographic healing is not significantly different.*

2. *Frequency of post-operative pain and flare-up is similar following single- and multiple-visit root canal treatment.*

3. *Patients overwhelmingly prefer single- over multiple-visit treatment.*

4. *Single-visit root canal treatment costs society less than multiple-visit treatment.*

The overall conclusion from these findings is that single-visit treatment is the preferred option whenever feasible. Of the above findings, only the first two require further comment. The conclusion that there is no difference in effectiveness of the two treatment regimens has been resisted by a number of authors (Spångberg 2001, Nair *et al.* 2005) and by a large majority of Australian endodontists (Chapter 6). The arguments against single-visit treatment of apical periodontitis are that the clinical studies are flawed (Spångberg 2007) (see Appendix IV), and that from a biological point of view adequate microbial control cannot be achieved in one visit (hence an inter-appointment antibacterial medicament is needed) (Spångberg 2001, Nair *et al.* 2005).
A total of five randomized clinical trials (Trope et al. 1999, Weiger et al. 2000, Peters & Wesselink 2002, Molander et al. 2007, Penesis et al. 2008) and one high quality prospective cohort study (de Chevigny et al. 2008) have now reported that no difference in healing was observed between single- and multiple-visit treatment of apical periodontitis. Three systematic reviews including a Cochrane review have, not surprisingly, drawn the same conclusion (Sathorn et al. 2005, Figini et al. 2007, Ng et al. 2008). No published high quality study has demonstrated a clinical benefit of multi-visit treatment.

The first systematic review derived from this thesis (Sathorn et al. 2005) was criticised in a recent editorial (Spångberg 2007) (see Appendix IV). The editorial argued strongly that the quality of included studies was questionable and opined that no conclusion can be drawn regarding the effectiveness of single- and multiple-visit root canal treatment because of the lack of good quality studies and bias. On the contrary, Figini et al. (2007), using Cochrane review standard criteria for assessing bias of clinical trials, rated 2 out of the 3 studies as “low risk of bias” and the third “moderate risk of bias”. The two randomized controlled trials published since then can also be rated as “low risk of bias” using the same criteria (i.e. appropriate sequence generation, appropriate allocation concealment, more than 80% recall rate, no selective outcome reporting).

Of course there are flaws in each study. No study is flawless, nor should it be expected (Elwood 1998, Marchevsky 2000). The real concern, however, is whether any flaws are likely to influence outcomes and to what extent, rather than simply disregarding the conclusions. Nonetheless, it must be
acknowledged that the number of cases is small (total n=298 in 5 randomized controlled clinical trials). A large multi-centre trial with strict criteria for healing is desirable, but given the small anticipated difference in healing (less than 10% based on studies to date), the number of participants would need to be extremely large. It is unlikely that such a trial, over a period of at least five years and achieving a recall rate of 80%, will ever be conducted. In fact, Endodontic Global Study proposed by Professor Friedman of the University of Toronto to investigate this very issue in a global scale was abandoned because of the lack of funding.

Post-operative pain and flare-up are transient and are unlikely to affect long-term outcomes. Post-operative pain has a high prevalence but low impact on individual patients, while flare-up has high (though transient) impact on patient lifestyle, but a very low prevalence. The greater frequency of analgesic use by patients undergoing single-visit treatment reported in one systematic review (Figini et al. 2007) probably reflects a precautionary approach rather than an as-needed approach. In terms of post-operative pain and flare-up, contemporary endodontic techniques have probably reached a practical limit. With a weighted average of 3% percent flare up rate (Walton & Fouad 1992, Imura & Zuolo 1995, Eleazer & Eleazer 1998), the possibility of further improvement is remote. Even if it could be improved (to 1 or 2%), it would be practically impossible to demonstrate statistical significance, as the required sample size for such a small improvement would be prohibitively high, i.e. more than 6000 patients (3% vs 2% expected flare-up rate at p=0.05, 80% power).
(Sokal & Rohlf 1995). Therefore, the merit of future studies on the issue must be questioned.

**ADOPTION OF CHANGE**

Despite the strong evidence in favour of single-visit treatment (although not all of the above information was available at the time of interview), a very large majority of Australian endodontists do not currently practise single-visit treatment routinely. Thus, the fifth finding of the study is:

5. *Australian endodontists are reluctant to embrace single-visit root canal treatment, notionally on biological grounds.*

Endodontists preferred multiple-visit treatment because of the perceived biological benefits, but were willing to perform single-visit treatment if there were time constraints and/or other logistical issues. Also, they were generally willing to consider single-visit treatment if biological concerns could be removed from consideration. Interestingly, the clinical evidence (which was largely available at the time of interview) did not appear to influence their preference. The difference between Australian and US endodontists is striking, with more than 70% of US endodontists embracing a single-visit approach (Whitten et al. 1996).

Decision making is a very complicated process. On the one hand, biological principles seemed to be very important to Australian endodontists when making clinical decisions, but on the other hand, logistical issues (practice management, convenience) tended to take precedence over these principles. Scientific data
published in peer-reviewed journals are insufficient to promote change or influence treatment decision making of clinicians. Peer influence seemed to carry more weight, which is in complete agreement with earlier studies of adoption of innovation (Rogers 2003, Greenhalgh et al. 2004).

The assumption that people behave or do not behave in a particular way purely because of lack of knowledge is most likely flawed (Haines & Donald 1998). The assumption has neither theoretical coherence nor empirical support. Simply imparting knowledge will, therefore, not necessarily change behaviour. Information may be necessary for change but it is rarely if ever sufficient. The key factors associated with a person’s readiness to change have been outlined (Greenhalgh et al. 2004). A number of personality traits are associated with the tendency to experiment and change, e.g. tolerance of ambiguity, motivation, and learning style. That is, certain people are inherently and innately more positive about change. A person who is motivated and capable of dealing with change is also more likely to change (Greenhalgh et al. 2004). The meaning that the change holds for the person also has a powerful influence on the decision to change.

It must be acknowledged that in the present context, standard innovation theory (Rogers 2003) may not be applicable. Single-visit treatment does not result in a better outcome with fewer adverse effects than multiple-visit treatment; rather, the two are comparable. Single-visit treatment is simply less time consuming, less expensive and preferred by patients. Thus, the impetus to change is reduced, unless there is also a perceived benefit to the provider (endodontist). The difference in materials costs, for example, was negligible. Thus, practice
organization, operator comfort and related considerations may predominate, although endodontists should at least consider offering patients a choice. From a broader resources point of view, single-visit treatment should be adopted to minimize cost and maximize delivery of care, which will be an important consideration from a public health perspective.

A CONFLICT IN DECISION-MAKING PHILOSOPHY: BIOLOGICAL RATIONALE VS. CLINICAL EVIDENCE

One of the principles of evidence-based health practice is that there is a hierarchy of evidence, with RCTs (and systematic reviews of RCTs) in the highest category, while expert opinion based solely on biological principles or laboratory research falls “below the line” (Sackett 2000). When two lines of evidence are in conflict, high quality clinical data should take precedence over scientific logic, and the reasons for the tension need to be explored further. Why is there a disagreement between clinical findings and “biological rationale”?

The biological rationale against management of apical periodontitis in one appointment (Spångberg 2001, Nair et al. 2005) is based essentially on three premises:

1. Bacterial eradication is essential for optimal healing.

2. Cleaning and shaping procedures (including the use of an antimicrobial irrigant) do not routinely eliminate bacteria.

3. Intracanal medicaments reliably achieve bacterial eradication.
These premises have two necessary corollaries, based on the use of bacterial cultures to monitor the microbial status of root canals: Firstly, culture of root canal samples accurately represents intracanal bacterial status, i.e. a negative culture equals absence of bacteria; and secondly, culture status is a reliable predictor of clinical outcome.

These issues have been addressed in part in the thesis (Chapters 7 and 8), and will be further considered here. It is clear that complete bacterial eradication is not essential for healing, and that a majority of cases with a positive culture at the time of obturation heal (Sjögren et al. 1997, Peters & Wesselink 2002, Molander et al. 2007). Indeed, no statistically significant difference in healing between teeth with positive and negative cultures was noted in two of these studies. The second premise has been well documented, with an average of approximately 60% positive cultures after cleaning and shaping (Chapter 7).

Analysis of the literature on intracanal medication, however, led to the sixth conclusion of this thesis:

6. Calcium hydroxide intracanal medication provides limited benefit in terms of bacterial elimination, as measured by culturing.

Intracanal medicaments (specifically calcium hydroxide) are of limited benefit (Sathorn et al. 2007), possibly because they are largely inactivated in the presence of dentine (Haapasalo et al. 2007). The meta-analysis taking into account culture reversals failed to demonstrate a significant effect of calcium hydroxide on the number of positive cultures, and three more recent studies have substantiated the conclusions of this thesis, i.e. calcium hydroxide
intracanal medicament does not significantly reduce the number of canals with positive cultures (Zerella et al. 2005, Manzur et al. 2007, Siqueira et al. 2007). In one of the studies (a re-treatment study; Zerella et al 2005), the number of positive cultures consistently increased following canal medication with calcium hydroxide, relative to culture status immediately after cleaning and shaping.

It is also becoming increasingly clear that culture results do not reliably represent actual intracanal bacterial status (Reit & Dahlén 1988, Molander et al. 1990, Reit et al. 1999). Thus, a biological rationale that depends on culture results must be considered seriously flawed. Stated simply, culture results are not a reliable predictor of healing or persistent disease.

**Cultures as a clinical outcome predictor (or surrogate endpoint)**

The accuracy of microbiological root canal sampling is low, and consequently is not reliable in determining bacterial status in the root canal. The implication of this assessment is summarized as the final conclusion of the thesis:

7. *Culture results based on current methods of intracanal sampling do not serve as a reliable predictor of clinical outcome.*

A surrogate endpoint is defined as a biomarker that is intended to substitute for a clinical endpoint (Burzykowski et al. 2005). A surrogate endpoint is expected to predict clinical benefit (or harm or lack of benefit or harm) based on epidemiologic, therapeutic, pathophysiologic, or other scientific evidence. Clinical endpoints, on the other hand, are distinct, direct measurements that reflect how a patient responds to treatment. Clinical endpoints are the most
credible characteristics used in the assessment of the benefits and risks of a therapeutic intervention in randomized clinical trials.

The most reliable way to assess the clinical impact of a novel technique is through its effect on a well-defined clinical endpoint such as healing of a radiographic lesion or survival of the tooth after endodontic treatment. However, this standard may be impractical for the evaluation of new therapies, because long periods are required for these clinical endpoints to be achieved and trials with large numbers of patients are needed for their evaluation. This is a major impediment in clinical research. Healing of apical periodontitis, for example, may take many years to show clearly on radiographs (Molven et al. 2002). For stringent success criteria, a follow-up time of four years has been used (Strindberg 1956) and is still advocated (Spångberg 2007). The issue of loss to follow-up has seriously compromised the reliability of many clinical studies, as a high proportion of subjects are unaccounted for. Therefore, high quality endodontic clinical trials using clinically meaningful endpoints are rare. The use of root canal cultures as a surrogate endpoint can expedite the trial process. However, it must be recognized that this is not an end in itself and that its merit is only as high as its ability to predict clinical outcomes. Culture results expressed simply in dichotomous terms (positive, negative) have only a very limited predictive value.

**Surrogate endpoint failures**

There are several models explaining the failure of surrogate endpoints (Fleming & DeMets 1996). Model 2 would probably best fit root canal cultures and healing of apical periodontitis (Figure 9.1).
Endodontic treatment procedures affect bacterial status, but healing does not depend solely on the presence of bacteria in canals. Sixty eight percent of canals positive to bacteria cultures healed completely (Sjögren et al. 1997). Also, there are several assessment criteria for the validity of surrogate endpoints that root canal cultures do not meet (Burzykowski et al. 2005).

**Strength of association:** A surrogate endpoint should preferably carry a strong and reproducible association to real endpoints in both a qualitative and quantitative manner. Only one small clinical study demonstrated such an association, with low strength (Sjögren et al. 1997). More recent studies reported no significant association (Peters & Wesselink 2002, Molander et al. 2007).
Reliability: A surrogate can only be valid if it is captured by a measurement, which is reliable and reproducible. The reliability of root canal cultures is greatly affected by medication, and results do not reliably represent actual intracanal bacterial status (Reit & Dahlén 1988, Molander et al. 1990, Reit et al. 1999). The association of culture results and healing rates is not reproducible across different studies (Sjögren et al. 1997, Peters & Wesselink 2002, Molander et al. 2007), and cannot be used predictively for individual patients.

Success in clinical trials: Data should be available from clinical outcome trials which test the hypothesis that changes in the surrogate will result in clinical benefits. As previously mentioned, only one small clinical trial showed such a correlation (Sjögren et al. 1997), but the other two showed failure (Peters & Wesselink 2002, Molander et al. 2007).

Concordance and parallelism: The intervention should have a similar qualitative effect and proportionality of change between the surrogate endpoint and a clinical endpoint exposed to different interventions, so that an estimate of clinical benefit can be reliably predicted by an estimate of change in the surrogate endpoint. Root canal culture studies mostly report only binary outcomes, i.e. positive vs negative bacterial culture. Bacterial load in the root canal has not been linked to healing rate.

Taken at face value, root canal cultures seem to be a good surrogate endpoint because bacteria are on the causal pathway (Kakehashi et al. 1965, Sundqvist 1976, Möller et al. 1981), and biological plausibility definitely exists. Under closer scrutiny, however, root canal cultures are not the perfect outcome
predictor as is often assumed. Whenever possible, choice of treatment regimen should be based on clear proof of \textit{clinical} benefit associated with lack of significant harm, provided by randomized controlled trials with clinically-relevant outcomes. In other words, the studies of clinically meaningful endpoints (healing of apical periodontitis) should outweigh the importance of studies using root canal culture as a surrogate endpoint.

Numerous intracanal medicaments or combinations thereof, clinical procedures and devices are evaluated based on microbiological root canal sampling. Until the root canal sampling technique can be improved so that it more accurately represents the actual root canal bacterial status, studies of this kind must be interpreted cautiously. The endodontic research focus should shift toward developing a better test method rather than trying to improve treatment protocols based on unreliable methodology. Use of the PAI (Ørstavik \textit{et al.} 1986) or digital subtraction radiography (Ørstavik \textit{et al.} 1990, Ørstavik 1991) has been proposed but neither is widely used and they have not been formally validated. There is an urgent need to address this issue, perhaps with the use of quantitative molecular markers of either microbial control or the host response.

\textbf{LIMITATIONS OF AN EVIDENCE-BASED APPROACH}

Clinical endodontic data are limited, and an evidence-based approach will provide only limited answers to important clinical questions. There are theoretical and practical limits to evidence-based practice. Theoretically, evidence-based practice addresses questions asking "what is the chance that" X benefits or harms people, not "how or why". This limits the application of
Discussion

evidence-based practice to an important, but defined, subset of questions in clinical practice and policy. For example, evidence-based medicine is helpful for deciding whether to carry out certain procedures, but it is not so helpful for finding out why certain materials behave the way they do. Practical limits usually involve absence of the support structures needed for sustained evidence-based decision making. Lack of commitment to its due process, insufficient evidence for too many problems, and insufficient local skills for interpreting evidence-based information can all limit the feasibility of evidence-based medicine in particular settings (http://www.medscape.com/viewarticle/430709_10 last accessed September 5, 2008).

The shortage of coherent, consistent scientific evidence is by no mean unique to dentistry. It is universally encountered in all areas of healthcare practice. Clinicians frequently find themselves in situations which there is no relevant evidence from either basic or applied research (Naylor 1995). Even when evidence exists, difficulties arise when it is inconclusive, inconsistent with previous studies, irrelevant to clinical realities or of poor quality. These limitations, however, are becoming much less marked as professional bodies worldwide develop such a resource. More clinical studies, particularly randomized controlled trials are being conducted and published. In dental journals alone the number of RCTs published has increased at almost exponential rates (Figure 9.2).
RCTs, however, are not a panacea. They do not provide any assurance that a particular treatment will produce the best outcome for a particular patient. While RCTs may demonstrate that more patients obtain a better outcome with treatment A than with treatment B in the long run, there is usually a minority of patients on treatment A who have worse outcomes than some patients on treatment B; this is reasonably acceptable from an epidemiological perspective, which takes a population as the unit of interest. The clinician, however, faced with an individual patient still has to assess whether treatment A or B will be better for that particular patient. Subgroup analysis may help in assessing the probability of benefit for an individual patient although the dangers of post hoc hypotheses (bias) are well recognized (Kemm 2006).

The type of trial considered "gold standard" (i.e. randomized double-blind placebo-controlled trials) may be impractical either because of the time and expense involved or because of the nature of the clinical condition being investigated. Studies of rare diseases are difficult to conduct. Treatment of dens invaginatus, for example, is too infrequent to be studied using a study...
design of high level evidence. All evidence related to the management of dens invaginatus is in the form of case reports or case series (Girsch & McClammy 2002, Brkic et al. 2003, Sathorn & Parashos 2007). The prognosis for canals containing fractured instrument fragments cannot be evaluated at a level higher than a case-control study (Spili et al. 2005). This emphasizes the point that the nature of the cases and treatment records should be documented meticulously and probably in a more systematic format, which will render future analysis possible.

Whether an evidence-based approach will thrive in endodontics depends largely on the quality of future clinical studies, given the limitations of the existing clinical literature. Adherence to CONSORT guidelines and the adoption of agreed, uniform criteria for outcomes (or development of a valid surrogate endpoint) will be necessary to ensure that a valid basis for optimal treatment is established.
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10 Appendix I Questions and Answers in Evidence-Based Patient Care

Questions and answers in evidence-based patient care.

An article published in

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This article provides a basic understanding and rationales of evidence-based concepts. It was written for readers who have not had prior exposure to these concepts.
Questions and answers in evidence-based patient care

C. Sathorn¹ and P. Parashos²

Evidence-based healthcare has become the mainstream of current healthcare practices, yet there seem to be many misunderstandings concerning this concept. This paper reviews several aspects of the concept of evidence-based healthcare in a simple question-and-answer format. The areas considered include: the significance of the evidence-based concept in clinical practice, the method of conducting a detailed electronic search of the literature, and the interpretation and application of research evidence to patients and immediate clinical applications.

INTRODUCTION

The concept of evidence-based healthcare has assumed major importance in providing optimal treatment modalities for patients.¹ From one perspective, ‘evidence-based’ is practically a buzzword in healthcare circles because it is spoken of, quoted, and used as a basis for clinical arguments. However, there appear to be many misunderstandings concerning the concept of evidence-based healthcare, and this may result in the term being abused. The purpose of this article is to dispel any confusion concerning the concept of evidence-based healthcare in a simple question-and-answer format covering concepts, methods, and interpretation with the ultimate goal of improved patient care.

1. WHAT IS EVIDENCED-BASED HEALTHCARE?

It is an integration of best available research evidence with clinical expertise and patient values.² When these three elements are combined, clinicians and patients form a diagnostic and therapeutic alliance which optimises clinical outcomes and quality of life.

2. WHY EVIDENCE-BASED?

Life is full of choices. What are we having for dinner tonight? Where are we going shopping tomorrow? These choices can be made simply by deciding what one wants. However, when we are faced with more complex situations, what we want is probably not enough. What brand of composite do we choose over another? Which treatment regimen should be offered to our patients and on what basis? We need solid foundations on which our decision-making process can rely. Evidence-based healthcare concepts suggest that these foundations are: 1) research evidence, 2) clinical expertise (eg operator capability and satisfaction) and 3) patient values (eg patient satisfaction, cost).

Clinicians are continually overwhelmed with an unmanageable amount of healthcare information from a variety of sources. In dentistry, there are over 500 journals publishing over 43,000 research articles a year.³ How do we cope with this amount of information and yet still be able to provide the current best available treatment to our patients? Evidence-based dentistry (EBD) can help, at least in part.

3. HOW DOES THIS CONCEPT HELP CLINICIANS AND THEIR PATIENTS?

It helps to improve the decision-making process making it more objective, consistent, and up-to-date. This ultimately improves the quality of treatment the clinician can provide and the level of healthcare for the patient.

4. HOW DO WE ACTUALLY PRACTICE EBD?

Essentially it consists of five steps:

a) Converting the need for information (about prevention, diagnosis, prognosis, therapy, causation, etc) into an answerable question
b) Tracking down the best evidence with which to answer that question
c) Critically appraising that evidence for its validity (closeness to the truth, impact (size of the effect),

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and applicability (usefulness in our clinical practice)

5. WHAT IS THE QUESTION?
Asking the right question is the first step in getting the right answer. The evidence-based concept suggests that the question should be formulated in the form of a PICO (Problem, Intervention, Comparison, and Outcome) question, which makes the question clearly defined and more likely to be answerable.

An example of such a question is: In patients undergoing endodontic treatment for apical periodontitis (teeth with an infected root canal system), does single-visit endodontic treatment without a calcium hydroxide dressing, compared to multiple-visit endodontic treatment with a calcium hydroxide dressing for one week or more, result in a lower healing (‘success’) rate (as measured by clinical and radiographic interpretation)? In this question the Problem is apical periodontitis, the Intervention is endodontic treatment; the Comparison is single and multiple-visit endodontic treatment, and the Outcome is healing rate of two treatment regimens.

6. WHAT IS EVIDENCE?
Simplistically, evidence is everything. Articles appearing in peer reviewed journals are evidence. Systematic reviews and randomised controlled clinical trials are evidence. Expert opinion or even our experiences with individual patients are evidence. The key is their order or their credibility as is explained below.

In order to determine what kind of evidence is more reliable consider the following comparisons.

6.1 Systematic study vs. clinical impression and/or experience
Bias cannot be controlled effectively in clinical impression and/or experience.
Operator bias: one clinician’s treatment outcomes are better than others. It has been shown that dentists are less likely to prescribe amalgam refilling of their own fillings compared to fillings
done by others. Radiographically, endodontic lesions tend to heal more promptly if the operators read their own films. This bias can be reasonably eliminated in systematic studies.

Population bias: patients are not randomly selected from the population and are not randomly distributed in the dentist’s interventions, and, so, generalisation or extrapolation to other clinician’s patients are unlikely to be valid. This bias can be reduced or eliminated in some study designs (e.g. randomised control trials).

In non-controlled environments (e.g. private practices) correlation and causation cannot be distinguished. For example, haemorrhagic fever prevalence is very high in the rainy season. Does rain cause haemorrhagic fever? A reasonable person would say ‘unlikely’. Because fever prevalence and quantity of rain correlate, that does not mean they are cause and effect. Factors affecting treatment outcomes are much more complex than this example. Clinicians can be deceived easily by correlation. For example, after using Product X in ten patients, the clinician finds that a week later all endodontic symptoms have disappeared. This is a desirable result, but what does it really mean? Does Product X resolve endodontic symptoms? Should we always use Product X? The truth is that it means nothing, or virtually nothing. The main reason is because there is no control group. Hence, it is not known whether without Product X all symptoms would have resolved anyway? Again, systematic studies in a controlled environment can reduce or eliminate bias and/or confounders.

6.2 Scientific logic
In dentistry, where clinical trials are expensive, time-consuming and not popular, good quality evidence is lacking. Direct evidence is generally unavailable. For example, sodium hypochlorite (NaOCl) has been used in endodontics for decades, yet we do not have direct evidence indicating the benefits of NaOCl in the improvement of treatment outcomes. Why do we still use NaOCl when direct evidence is lacking? The answer is scientific logic. Although direct evidence is lacking, and the association of treatment success with the use of NaOCl has never been established, this does not preclude us from logical thinking.

Here is an example of a simple logical thought process: Apical periodontitis is caused by bacteria. Removal of the cause should cure the disease. This notion is also substantiated by a study showing that bacteria-negative canals have a better chance of healing (disease cured). NaOCl can eliminate bacteria. Therefore, because the cause is removed, the disease should then be cured. This thought process is termed scientific logic. This is also considered evidence. In dentistry, scientific logic is used extensively because direct evidence is scarce, albeit much more reliable and more clinically relevant.

6.3 Clinical vs. laboratory studies
Of the articles published in the Journal of Endodontics during 1989-1990, 21.3% were laboratory leakage studies. This figure indicates that leakage studies comprise a major part of endodontic research, and this is likely to be true even now. The results of those studies can be so contradictory that very few conclusions can be drawn, if at all. For example, one laboratory study concluded that root canals can be completely contaminated after bacterial challenge in 19 days. But what does this actually mean clinically? Does it mean retreatment of every root canal after gutta-percha is exposed to saliva for 19 days? A clinical study, on the contrary, has shown otherwise, specifically that the loss of the coronal restoration had little impact on the healing rate or endodontic success. Even though the sample size was much too small to draw a definite conclusion, the data in this paper suggested (and only suggested) that the problem of coronal leakage may not be of such great clinical importance as implicated.
by numerous laboratory leakage studies, provided instrumentation and root filling are carefully performed. Most bacterial leakage studies can only indicate whether there is bacterial leakage and how soon leakage occurs. Furthermore, one bacterium or 10,000 bacteria differ greatly in terms of disease-causing potential. Another significant point that a laboratory study can never be able to take into account is the host defence mechanism. The human body is extraordinarily complex, and it is impossible to completely and accurately simulate clinical conditions in bench top studies. Although bench top studies have many advantages, clinical studies are more appealing and more relevant, especially to clinicians.

6.3.1 Clinical studies: what kind?
Basicallly, clinical studies test the association between a factor (X) and an event (Y) and if it exists, how strong is that association (Fig. 1)?

6.3.2 Why is the randomised controlled trial the gold standard?
This design can minimise confounders, which are 'hidden' variables in a study that affect the variables in question but are not known or acknowledged, and thus (potentially) distort the resulting data. This design can also minimise control over the environment providing the most convincing causal relationship.

6.4 Hierarchy of evidence or quality of evidence (Fig. 1)
The following order is considered:
1. Systematic review and meta-analysis
2. Randomised controlled trial (RCT)
3. Cohort studies
4. Case control studies
5. Cross-sectional surveys
6. Case series or case reports
7. Expert opinion.

6.5 What is the basis for this hierarchy?
- The systematic review represents the highest quality evidence because it is a summation of the current best quality checked individual studies
- The design with randomisation can minimise confounders and selection bias because it leaves only chance to play a role in deciding which subject receives what treatment
- The design with a prospective nature allows researchers to have more control over the environment
- Treatment and disease effects take time to develop, therefore the design with no time element (eg. cross-sectional surveys) has limited ability to differentiate between cause and effect
- There is no control group in a case series or case report. It is merely a report of an event, which can be caused by several undetermined factors
- Expert opinion is difficult or virtually impossible to critically appraise.

6.6 Peer-reviewed journals: why?
Articles published in peer reviewed journals have been scrutinised by referees, who usually are experts in that particular area. Chances are that seriously flawed studies are less likely to pass through the review process and be published in these journals, but this is not always the case. In view of evidence-based concepts, articles should be critically appraised according to their merits (quality of their study design, materials and methods) rather than in what journal they are published.

"Grey" literature represents articles published in non-peer-reviewed journals eg. Dentistry Today, Australasian Dentist. Academically, they are considered low in value. However, in strict adherence to evidence-based concepts, grey literature should be identified and included in the analysis. Such literature can be excluded from analysis only because of merit and not merit alone. It should not be excluded because it is not peer-reviewed.

6.7 How do we know that a journal is peer-reviewed?
Bowler's Ulrich's website http://www.ulrichsweb.com/UlrichsWeb/ is a website designed for the convenience of librarians regarding purchasing and organizing journals. This site contains journal details such as publishers, country of publication, subscription fee, and also whether the journal is refereed or peer-reviewed.

7. WHERE CAN THE EVIDENCE BE FOUND?
The significance of locating an available and relevant evidence cannot be over emphasised in the evidence-based concept. The current best available evidence should dictate clinical decision-making and, in fact, is the very foundation of the evidence-based concept. To obtain current best available evidence, all relevant evidence must be located, critically appraised and ranked.

Relying on one or a few studies as the basis for treatment recommendations is not very prudent. A useful analogy is the series of clinical studies comparing the effects of quality of obturation and restoration (apical vs. coronal seal on healing, in the first such study Ray and Trope concluded that the quality of the coronal restoration was significantly more important than the quality of endodontic filling to treatment outcome (P < 0.001, Chi square test) (odds ratio = 2.6, 95% CI; 1.8 to 3.9). However, a succeeding article reported the completely opposite result. When five studies investigating the same issue were identified and were statistically combined, a different picture emerged. The highly significant result in Ray and Trope then became non-significant (P = 0.55) with odds ratio of 0.8 (95% CI: 0.3 to 1.8) (meta-analysis data using the random effect method, RevMan Version 4.2.7). Therefore, the quality of the coronal seal is as important as the quality of the apical seal to treatment outcome, and both have an equal impact on prognosis. This emphasizes the point that one study is not sufficient, and that all relevant evidence must be identified.

7.1 Databases
7.1.1 The Medline database
This is a database of biomedical citations and abstracts. Medline covers over 4,800 journals published in the United States and more than 70 other countries primarily from 1966 to the present. Medline includes references to articles indexed with terms from the National Library of Medicine's controlled vocabulary, MeSH (Medical Subject Heading). Citations in Medline are from journals selected for inclusion in the database. Essentially, Medline is the most popular and the most comprehensive database for healthcare information, and citation information is electronically accumulated every day. There are several search service providers sharing the same Medline database eg Pubmed, Ovid Medline, SilverPlatter etc. Pubmed is a website providing free services using the Medline database, and is made possible by the National Institute of Health.
of the USA. It is the starting point for every search, but for complex search strategies, there are some limitations on Pubmed, and so Ovid Medline may be a better place to run such a search.

7.1.2 The EviDents search engine
http://medinformatics.uthscsa.edu/
EviDents/
This is a search engine designed specifically for evidence-based dentistry by the University of Texas. It is a complex Medline search strategy made simple by embedding pre-designed search strategies in the EviDents webpage, and the user simply clicks the form. It has benefits from a practical viewpoint, but the benefits are limited, because there are very few good quality clinical studies in dentistry. Also, the pre-designed search strategy is quite sensitive in some areas resulting in far too few studies matching their criteria.

7.1.3 The Embase database
This is a Medline counterpart, but is a European initiative. It has better coverage of non-English languages and European based journals. Articles in Embase are assigned more index terms than those in Medline, and consequently people using Embase may be less likely to miss an important article but must spend more time browsing through irrelevant material. The overlap of journals in the Medline and Embase databases is about 34%, and it has been shown that using both improves the coverage of the literature.

Embase complements Medline and vice versa. To retrieve important articles that are not indexed in Medline, it is essential to use Embase in searches conducted for a comprehensive review, or to find rare case reports. Embase is more expensive, more time consuming to use, and perhaps less accessible than Medline. For information about drugs and therapeutics, Embase should be used, and especially when Medline has not retrieved sufficient information or when more comprehensive coverage of the literature is required. From a dental perspective, however, Embase has few advantages over Medline.

7.1.4 The Science Citation Index database
A unique feature, which does not exist in other databases, is that this index can find follow-up work done on a key article. This process is called a secondary search. This feature is beneficial when a definitely relevant article (key article) has been located, and subsequent papers can be traced. Chances are that if the later article tried to answer the same questions as the earlier article, the earlier article should be cited by the later one.

7.1.5 The Cochrane library database
The Cochrane library provides systematic quality checked summaries of all the evidence on a particular topic. Theoretically, a search should start here because this database contains the most up-to-date and the most methodologically stringent systematic reviews and meta analyses. Because dentistry was left far behind in the evidence-based movement, currently, this database has little benefit, if any, in the dental field. Nevertheless, for the sake of completeness and comprehensiveness, all mentioned databases should be searched thoroughly.

7.2 How to locate evidence
This section summarises the basic technique which has been detailed by a series of articles.

In the Medline database an article is indexed using specific rules by the National Library of Medicine (NLM) of the USA. The indexing information is supplied by publishers and is also generated electronically by NLM. To track
down an article, one needs to guess what words the authors would have used or what words would appear in the citation information. To search comprehensively, all possible words that might be used need to be considered.

Further, search adjuncts, such as Boolean operators (Fig. 2), provide assistance and some control during literature searches. Boolean (named after logician George Boole) is a term used in mathematics, logic and computer science, and represents an expression with two possible values, ‘true’ and ‘false’. The most common Boolean functions are AND, OR, and NOT. For example, a ‘calcium hydroxide AND bacteria’ search strategy will show articles containing these two words in the same article. A ‘calcium hydroxide OR bacteria’ search strategy will show articles containing either the word calcium hydroxide or bacteria. A ‘calcium hydroxide NOT bacteria’ search strategy will show articles containing the term calcium hydroxide without the word bacteria.

Truncation symbols (also known as Wildcards) are symbols used to represent various characters, and the asterisk symbol (*) is a commonly used wildcard. For example: stabilis” would include stabilisation OR stabilising OR stabilised (ie any words with any characters following ‘stabilis’ will be detected and shown in the search).

7.2.1 Locating an article already known to exist
For example, to retrieve the full text article by Love (1996) on how deep bacteria penetrate into dentinal tubules, the following sequence is followed (Fig. 3):
1. Go to the PubMed website
2. Click ‘Limit’
3. Type ‘love’ in the bar
4. Click the drop down list of ‘All Fields’ and select ‘Author’
5. Enter publication date from 1996 to 1996
6. Click the drop down list of ‘Subset’ and select ‘Dental Journals’.

The resulting screen shows nine articles that match the search criteria, and browsing these reveals article number 7 as the required paper (Fig. 4).

7.2.2 Answering a very specific question
For example, does routine reducing the occlusion of teeth undergoing endodontic treatment reduce the chance of interappointment pain? Thus, to find every article that relates occlusal reduction to endodontics, the following sequence is indicated:
1. Go to the EvI Dents website (Fig. 5)
2. Type ‘occlusal reduction’ in the ‘Problem’ bar
3. Click ‘Endodontics’ in ‘Clinical area’
4. Leave the other options in the default settings
5. Click ‘Search’
6. The EvI Dents site will link to the PubMed website showing eight articles (Fig. 6).

After browsing through these articles, the article that is most likely to give an answer would be article number 4. Namely: The effect of occlusal reduction on pain after endodontic instrumentation. I Fadad 1998; 24: 497-496.

The abstract of this paper indicates the study design to be a randomised controlled trial, which provides the most convincing causal relationship between occlusal reduction and pain (or the reduction of pain) after endodontic treatment. Therefore, this could be a key article. To make the search more comprehensive, a secondary search is run on this article in the Science Citation Index database, to determine what articles were cited by this key article and also what articles have cited this key article (Fig. 7).
Questions and Answers

1. Copy the title of this key article from the PubMed website
2. Go to the Science Citation Index website
3. Paste the title in the box at 'Quick search'
4. Click 'GO'
5. This key article will appear, then click on this article (Fig. 8)
6. The next page will show that this key article has 11 references, and this key article is cited by three articles (Fig. 9)
7. Check all 16 articles
8. Two more potentially relevant articles will be presented, which need to be verified by full text only.

- Title: Effect of occlusal relief on endodontic pain
  Author(s): Crecy JL, Walton KE, Kaltenbach R
- Title: The effect of occlusal reduction after canal preparation on patient comfort
  Author(s): Innes KJ, Holland GR

After this comprehensive search, finally, there are three articles to read and from which to obtain information.

2.2.3 Obtaining general information quickly about a well defined topic
For example, to obtain information about biofilms:

Make use of MeSH terms:
1. Go to PubMed
2. Type biofilm[mh] any articles which have been indexed in Medical Subject Heading as biofilm will appear. The Medical Subject Heading or MH is the National Library of Medicine’s controlled vocabulary used for indexing articles for MEDLINE/PubMed. MeSH terminology provides a consistent way to retrieve information that may use different terminology for the same concepts. The benefit of using MeSH terms is that even if the citation information and abstracts of articles do not contain the word ‘biofilm’, the articles will still be detected if they are related to biofilm
3. The result is 3,855 articles, which is too many and so the search results need to be refined
4. Click ‘limits’ (Fig. 10)
5. Click drop down list of ‘Type of Article’, select ‘Review’ – any articles that are indexed as review will be detected
6. Click drop down list of ‘Languages’, select ‘English’ (or other if appropriate)
7. The result is now 495 articles which is still too many; refine it again
8. Click drop down list of ‘Subsets’, select ‘Dental journals’
9. The result is 88 articles, but this is still too many. If only one article giving general information of biofilm is required, refine the search again
10. Change biofilm[mh] to biofilm*[ti] – any articles which contain biofilm or biofilms in the title will be detected this time. Full is a computer term used here to instruct the search engine to look only in the title.
11. The result is 29 articles, which is now acceptable, and browsing all of them indicates a few potential articles but the most likely key article would be number 13. Namely: Dental biofilms: difficult therapeutic targets. Periodontol 2000 2002; 28: 12-55.

Periodontology 2000 is a journal exclusively for review articles, where authors are invited to submit their
PREREVIEW

articles by the editors of each issue. These authors are experts in their fields and their articles are most likely to give a general idea of biotrans.

2.2.4 What to do when a number of relevant articles are retrieved
In this case a Boolean ‘NOT’ could be used to exclude irrelevant articles. The initial search strategy in Sathorn et al.4 gave hundreds of articles which contained the term single, multiple, appointment and endodontics. Most of them were articles comparing flare-up rates, which, of course, were not relevant. To exclude flare-up studies from the initial results, ‘NOT’ was added in search strategy by typing ‘NOT flare up’ in the bar. The result will then be narrowed down.

8. HOW TO CRITICALLY APPRAISE EVIDENCE

Once all available evidence has been located, the next step is to ascertain whether the evidence can be trusted and is relevant.

The single most important element of evidence appraisal is probably common sense, which takes time and effort to develop fully. For beginners of evidence appraisal, the following can serve as aids.

8.1 CASP

http://www.phru.nhs.uk/casp/casp.htm

The Critical Appraisal Skill Program (CASP) is a program developed by the National Health Services of the U.K. It aims to enable individuals to develop the skills to find and make sense of research evidence, helping them to put knowledge into practice. This program has developed critical appraisal tools for different kind of studies. These tools can be downloaded from http://www.phru.nhs.uk/casp/appraise.htm.

The tool consists of a series of questions, which are adapted largely from Guyatt et al.7 CASP, however, has made the questions succinct, concise and simple for beginners. By trying to answer every question in a critical appraisal tool not only will readers be able to determine the credibility of the paper, but they will understand the paper more thoroughly.

8.2 CONSORT guidelines

http://www.consort-statement.org/

A group of scientists, epidemiologists and editors developed the CONSORT (Consolidated Standards of Reporting Trials) statement, mainly to improve the quality of reporting of RCTs. For a full explanation of CONSORT, please visit the above website or refer to Altman et al.44 Many leading medical journals and major international editorial groups have adopted the CONSORT statement including the Journal of Endodontics and the International Endodontic Journal. The CONSORT statement facilitates critical appraisal and interpretation of clinical study by providing guidance to readers about what should be present in a good quality clinical trial.

9. CAN THE RESULTS FROM RESEARCH EVIDENCE BE IMMEDIATELY APPLIED?

‘Not quite’ is probably the answer.

9.1 Patient

First of all, one must ask oneself whether the particular patient would be included in the studies. If this patient will be included, then the conclusion from the evidence can and should be applied to this patient. For example, in Sathorn et al.4 one of the exclusion criteria was retreatment cases. That means that if the patient required endodontic retreatment, then this patient would be excluded from the study, and as a result, conclusions from Sathorn et al.4 should not be applied to this patient. Basically, the inclusion and exclusion criteria of the studies should be applied to the particular patient, and if applicable, then the patient may benefit from the conclusions of the evidence.

9.2 Operator

Again, the clinician should ask, whether s/he could be one of the operators in the studies. In Sathorn et al.4 it is made clear that to apply the conclusions in the paper to one’s patients, the operator should be certain to provide the same treatment standard as the operators in the studies. Operator skill will always be an issue because different operators possess different levels of dexterity.

9.3 Patient’s unique values

Our patients are human and they have preferences. Treatment effectiveness might not be their highest priority. For example, in cancer treatment, a highly effective treatment protocol could deteriorate a patient’s quality of life a great deal. A patient might choose quality of life over treatment effectiveness, and we as professionals should respect their autonomy.

9.4 Patient circumstances

Identical patient, doctor and environment, but different circumstances could result in different treatment regimens. For example, although MTA apexification lacks clinical evidence supporting its benefits, it could and probably should be the treatment of choice in patients of low compliance especially with time constraints.

SUMMARY AND CONCLUSIONS

The evidence-based concept is a thought process designed to find the truth, or what is as close to the truth as possible, and makes the full use of it in clinical practice. It makes research evidence and literature more relevant to clinicians. Importantly, it asks more from the clinicians: not only must they master their clinical skills, and manoeuvre their manual dexteritys, but also their decision-making has to be logically and scientifically justifiable.

Questions and Answers

11 APPENDIX II PATIENT PERCEPTION QUESTIONNAIRE

The questionnaire used in chapter 4 is presented here.
Endodontic Treatment Questionnaire

Directions: The following five questions relate to how you felt about your treatment. Answer the followings questions in terms of how you felt.

1. Circle the number that best indicates how you felt

<table>
<thead>
<tr>
<th>Question</th>
<th>None</th>
<th>A little</th>
<th>Some</th>
<th>Quite a bit</th>
<th>Lots</th>
</tr>
</thead>
<tbody>
<tr>
<td>a) Did you feel faint or uncomfortable during or after the treatment?</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>b) How much difficulty do you have in opening your mouth after the treatment?</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>c) Have your neck, back or jaw ever ached before the treatment?</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>d) Did your neck, back or jaw ache during or after the treatment?</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>e) Did the treatment make you feel claustrophobic?</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>f) Did you feel that the appointment was too long?</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
</table>

2. At its worst, how would you rate your degree of discomfort during the treatment? Circle the number to indicate the severity of the degree of discomfort at its worst, when ‘zero’ is none and ‘ten’ is the highest you can imagine.

<table>
<thead>
<tr>
<th>Rating</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>10</th>
</tr>
</thead>
</table>
3. Please circle the number which most accurately represent your feeling concerning the following aspects of your experience.

<table>
<thead>
<tr>
<th></th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>10</th>
</tr>
</thead>
<tbody>
<tr>
<td>Expensive</td>
<td>Inexpensive</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time consuming</td>
<td>Quick</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Painful</td>
<td>Pain free</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unpleasant</td>
<td>Pleasant</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

I was...

<table>
<thead>
<tr>
<th></th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>10</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very dissatisfied</td>
<td>Very satisfied</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

4. If you had a choice, without affecting the results, which type of treatment would you prefer... (Please tick one box only)

- Treatment A: One long appointment to complete the entire procedure.

Imagine doubling your appointment time if your root canal treatment actually took 2 appointments.
Patient Questionnaire

☐ Treatment B: Two or more shorter appointments with at least a week apart to finish the treatment.

Imagine reducing your appointment time in half, if your root canal treatment was actually completed in one visit.

5. Please place a mark (X), in the following lines representing time periods.

   a) The longest appointment you would be willing tolerate.

   0 hour    1 hour   2 hour            3 hour


   b) What you think is the best length of appointment to suit you.

   0 hour    1 hour   2 hour            3 hour


6. Do you have any other comments you might want to add about the treatment?
7. How **long** did it take you to travel from your home to this practice?
12 Appendix III Detailed Cost Breakdowns

This appendix provides details of items and unit cost, in case the analysis were to be repeated in a different setting using the same calculation structure.
### TABLE I CLINICAL COST

<table>
<thead>
<tr>
<th>Clinical Assumption</th>
<th>Single-visit treatment</th>
<th>Multiple-visit treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Disposables</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>gloves</td>
<td>4.09/100pairs=4/visit</td>
<td>55.64</td>
</tr>
<tr>
<td>radiograph</td>
<td>double film*4</td>
<td>2.2</td>
</tr>
<tr>
<td>L.A.</td>
<td>29.68/50</td>
<td>0.59</td>
</tr>
<tr>
<td>needle</td>
<td>11.40/100</td>
<td>0.11</td>
</tr>
<tr>
<td>Orthoband</td>
<td>2.78</td>
<td>2.78</td>
</tr>
<tr>
<td>sheath</td>
<td>8.27/36@</td>
<td>0.23</td>
</tr>
<tr>
<td>burs</td>
<td></td>
<td>2.61</td>
</tr>
<tr>
<td>file create guiding path</td>
<td>5.65/6 use 2</td>
<td>1.88</td>
</tr>
<tr>
<td>2 or more ProFile</td>
<td>53.15/6 use 2</td>
<td>17.72</td>
</tr>
<tr>
<td>main cone fit</td>
<td>16.66/120 use 4 for molar</td>
<td>0.56</td>
</tr>
<tr>
<td>paper points</td>
<td>7.65/180 4 canals 4@</td>
<td>0.68</td>
</tr>
<tr>
<td>lentulo</td>
<td>13.37/4</td>
<td>3.3</td>
</tr>
<tr>
<td>accessory cone</td>
<td>16.66/120 6@/canal=24</td>
<td>3.3</td>
</tr>
<tr>
<td><strong>Materials</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Milton</td>
<td>5.02/1L use 20ml</td>
<td>0.1</td>
</tr>
<tr>
<td>EDTA</td>
<td>22.21/300ml use 5ml</td>
<td>0.04</td>
</tr>
<tr>
<td>sealer</td>
<td>105.73 8g powder 10gm resin</td>
<td>1.1</td>
</tr>
<tr>
<td>cavit</td>
<td>11.3/28g jar</td>
<td>0.18</td>
</tr>
<tr>
<td>Fuji IX</td>
<td>76.43/50 caps</td>
<td>1.53</td>
</tr>
<tr>
<td><strong>Small instruments</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>syringe</td>
<td>95.4/3yr LE=0.01/hr</td>
<td>0.03</td>
</tr>
<tr>
<td>clamp</td>
<td>11.86/ 2yr LE=0.003/hr</td>
<td>0.01</td>
</tr>
<tr>
<td>frame</td>
<td>13.36/ 3yr LE=0.004/hr</td>
<td>0.01</td>
</tr>
<tr>
<td>forceps</td>
<td>96.14/ 3yr LE=0.02/hr</td>
<td>0.05</td>
</tr>
<tr>
<td>endo explorer locate canal</td>
<td>26/ 2yr LE=0.007/hr</td>
<td>0.02</td>
</tr>
<tr>
<td>spreader</td>
<td>26/ 2yr LE=0.007/hr</td>
<td>0.02</td>
</tr>
<tr>
<td>plastic instrument</td>
<td>23.15/ 2yr LE=0.006/hr</td>
<td>0.02</td>
</tr>
<tr>
<td><strong>Major equipment</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dental Unit</td>
<td>ADEC 500 38365/ 10yr LE=2.05/hr</td>
<td>5.58</td>
</tr>
<tr>
<td>X ray machine</td>
<td>7175.3/10yr LE=0.38/hr</td>
<td>1</td>
</tr>
<tr>
<td>Airotor</td>
<td>1000/ 3yr LE=0.18/hr</td>
<td>0.48</td>
</tr>
<tr>
<td>slow speed</td>
<td>1200/ 3yr LE=0.21/hr</td>
<td>0.58</td>
</tr>
<tr>
<td>Scaler</td>
<td>900/ 3yr LE=0.16/hr</td>
<td>0.44</td>
</tr>
<tr>
<td>microscope</td>
<td>17000/ 3yr LE=0.91/hr</td>
<td>2.47</td>
</tr>
<tr>
<td>apex locator</td>
<td>3534/ 4yr LE=0.47/hr</td>
<td>1.28</td>
</tr>
<tr>
<td>triauto zx</td>
<td>2934/ 3yr LE=0.52/hr</td>
<td>1.42</td>
</tr>
<tr>
<td>system B</td>
<td>2300/ 5yr LE=0.27/hr</td>
<td>0.73</td>
</tr>
</tbody>
</table>

(LE=life expectancy)
## TABLE II OVERALL COST

<table>
<thead>
<tr>
<th>Costs</th>
<th>Assumption</th>
<th>Cost SV</th>
<th>Cost MV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical cost (Table1)</td>
<td></td>
<td>72.73</td>
<td>109.22</td>
</tr>
<tr>
<td><strong>Salaries</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Endodontist salary</td>
<td>86.94/hr</td>
<td>236.50</td>
<td>401.70</td>
</tr>
<tr>
<td>Nurse salary</td>
<td>16.60/hr</td>
<td>45.15</td>
<td>76.70</td>
</tr>
<tr>
<td><strong>Patient-related</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>full fee (co-payment + government subsidy)</td>
<td>1025</td>
<td>1025</td>
<td>1025</td>
</tr>
<tr>
<td>opportunity cost treatment</td>
<td>29.34/hr</td>
<td>79.80</td>
<td>135.55</td>
</tr>
<tr>
<td>opportunity cost traveling</td>
<td>1.13/hr one way</td>
<td>66.31</td>
<td>132.62</td>
</tr>
<tr>
<td><strong>Overheads (DHSV)</strong></td>
<td>Per year for Endo Unit (6 chairs)</td>
<td>62.51</td>
<td>106.16</td>
</tr>
<tr>
<td>Rent</td>
<td>1600/3units/mt=3.41/hr</td>
<td>9.28</td>
<td>15.75</td>
</tr>
<tr>
<td>Fit out</td>
<td>150k/ 15yr LÉ=5.33/hr</td>
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13 Appendix IV Criticisms

Series of articles published in

Oral surgery, oral medicine, oral pathology, oral radiology, and endodontics

2007;103(6):723-4

2007;104(3):303-4; author reply 304-6

2007;104(6):730; author reply 730

Evidence-Based Dentistry 2006;7(1):13-4

A conflict in decision-making philosophy can be better appreciated by following these series of articles.
Systematic reviews in endodontics—examples of GIGO?

In many areas of medicine the amount of published information is increasing at an exponential rate, making it difficult for the clinician to condense the data to a manageable amount of valuable and useful information. Systematic reviews have been suggested as a remedy for this information overload.¹ Such reviews are regarded as the highest level of evidence. Certain statistical methods, e.g., meta-analysis, have also been introduced for the calculation of a more comprehensive summation of the compiled results from studies with small sample sizes. These findings would then serve as an authoritative guide for evidence-based practice.

Endodontists have lately jumped on the bandwagon of systematic reviews and meta-analyses, and papers on various topics are being published. Well done, such comprehensive information would be very useful and authoritative for the practitioner. Alarmingly, the quality of these recent publications is negatively correlated to the frequency. This can have serious consequences in the clinical arena if spurious information is given a seal of approval when communicated as facts in refereed journals.

A systematic literature review is designed to focus on a single question and to synthesize all high-quality research reports relevant to the question. In these studies, however, sources of bias are often not controlled. Therefore, even the best review and meta-analysis becomes useless if it is based on poorly designed research. Furthermore, these reviews are mostly based on published data which are too often biased toward studies that show significant differences in results and/or outcome. “Uninteresting” conclusions tend not to be published.² Endodontic literature, thus far, is short on well designed and executed randomized clinical trials. Furthermore, clinical protocols often have many important “proprietary” modifications that make comparison difficult. This makes it very hard to undertake a systematic review to answer a narrow question. Such GIGO (garbage in, garbage out) can easily lead to biased conclusions and reinforce already existing biased conclusions.

An example of such bias can be illustrated by a meta-analysis recently published.³ The study focused on assessing if there were differences in outcome between 1 and 2 treatment visits when treating teeth with apical periodontitis. Relevant publications on this topic are rare, and with the narrow inclusion criteria only 3 investigations were available for the review.⁴,⁶ However, the only factors connecting these 3 studies was the words “single” and “two visits” in the title. Beyond that, the selected studies are too different and inadequate for the study. Only 1 study is somewhat demonstrably randomized,⁴ and outcome assessments are based on 3 vastly different criteria. Two of the studies⁵,⁶ use calcium hydroxide as intracanal dressing, whereas the third⁴ uses no intervisit medication. Complexity of initial pathology and healing time are also clearly factors of great importance but not controlled. In addition, sample sizes in the component studies as well as the final cohort are all too small for the conclusions that there was no significant difference between 1- or 2-visit treatment protocols. To undertake and publish a meta-analysis on such an incomplete sample is counterproductive. Although the publication noted its numerous limitations, it will still communicate erroneous conclusions with a poor scientific foundation to the less informed reader.

There are other examples of recently published systematic reviews that are very ambiguous and tend to communicate spurious facts.⁷,⁸ One of these studies⁷ looks at the effect of smear-layer removal on sealing ability of root canal obturation.⁷ The study is entirely limited to laboratory experiments, with the majority of evaluations using dye leakage which is generally considered to be unreliable. This is an example of reviewers lacking content expertise. The authors draw the conclusion, using defective review material, that removal of smear layer enhances the seal of the root filling. We may generally believe that this is the truth,
but there is absolutely no universal answer to this question in the selected literature. Another study looks at differences in treatment outcome between teeth filled with cold lateral condensation or warm gutta-percha. This study, too, searched for documentation that in general is unavailable in the mainstream endodontic literature. The authors were able to find some low-quality studies from very obscure journals. To compare and combine studies on obturation, it is very important to control treatment protocol details, such as diagnosis, asepsis, antisepsis, and instrumentation, all of which have significantly greater effect on treatment outcome than root filling technique. There is no such critical information available in the very heterogenic studies selected, and therefore data can not be combined to study the defined question. Follow-up time for 3 of the 10 studies mentioned is listed as 0, which makes for a poor outcome study. The conclusion of this study is once again the result of a poorly designed and executed systematic review.

The 3 studies described are examples of, respectively, biased sampling, lack of scientific insight, and poor understanding of topic content. A systematic review is not easy to do, and a great deal of work is required in combination with a substantial portion of common sense. Adequate literature to review and logical questions to ask must precede a review. There is also a real need that the reviewer(s) have significant training in research methodology and a good understanding of the content area studied. So why have I picked out these 3 articles, and why is it a big deal? We are all told to follow available evidence when practicing dentistry. Therefore, it is of utmost importance that publications in refereed journals are just that—seriously reviewed. The 3 articles given as examples will confuse the uninformed reader as being the facts. Only if the reader is very familiar with the endodontic literature is it possible to see these studies and their conclusions as inadequate.

Lacking randomized controlled trials, which are the gold standard, it is probably better to focus on some of the good observational studies available. Good clinical endodontic literature is still infrequent and it may still be a while before it can support authoritative clinical meta-analysis projects.

Lars S. W. Spangberg, DDS, PhD
Section Editor, Endodontontology

doi:10.1016/j.tripleo.2007.03.052

REFERENCES
LETTERS TO THE EDITOR

Systematic reviews in endodontics

Dear Dr. Spängberg,

Your recent editorial (“Systematic reviews in endodontics—examples of GIGO?” Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2007;103:723–4) was very thought provoking. The editorial was highly critical of 3 recent systematic reviews, and also of the “poorly designed research” that characterizes much of the clinical endodontic literature. Since all of the reviews were published in peer-reviewed journals (as were most of the papers included in the meta-analyses), surely part of the blame lies with reviewers, and with the editors who oversaw acceptance and publication of such papers?

Our recent systematic review1 enjoys the dubious distinction of first place in your honor roll of “garbage in, garbage out (GIGO).” Our review considered the evidence for a difference in healing frequency following root canal treatment in one versus multiple visits, and concluded that “current best available evidence failed to demonstrate a difference between the 2 treatment regimens.” We share your concern that biased analysis will confuse the uninformed reader. To that end, we wish to address a number of the points you have raised in your editorial.

1. Publication bias. The editorial correctly noted the risk that “uninteresting” conclusions tend not to be published, which may bias available data toward a particular outcome. Statistical techniques are available to test for publication bias, but the number of studies in our review was too small for such analysis. We addressed this issue in the Discussion. In any case, all 3 of our included studies showed no statistically significant differences in healing between single- and multiple-visit treatment. As also noted in our review, of the remaining 5 papers2–5 comparing clinical outcomes of the 2 treatment approaches (which we excluded because they were not randomized), not one reported a significant difference in outcomes. Friedman et al.6 came to statistical significance ($P = .05$), with better healing after single-visit treatment. It is difficult to believe that a significantly better outcome of either single- or multiple-visit treatment would be considered “uninteresting” and not worthy of publication.

2. Our paper was cited as an example of biased sampling, with excessively narrow inclusion criteria that limited the analysis to only 3 published studies. The implication is that we omitted relevant papers. The contention that “the only factors connecting the 3 studies were the words ‘single’ and ‘two visits’ in the title” is incorrect. The initial search strategy was based on key words that included “single,” “one,” “two,” and “multiple” “visits” or “appointments” anywhere in the Medline indexing information, which includes the title, abstract, MeSH terms, and so forth. Our paper also clearly states that subsequent search methods included scanning the reference lists of identified articles, forward searches in 3 databases for related papers, and a search of Science Citation Index for papers that had quoted the identified articles. We would be very appreciative (although somewhat chagrined) if you could kindly identify papers that we overlooked in our review. All we ask is that any such papers compare healing following single- and multiple-visit treatment in the same study.

3. Randomization. It is a misstatement that “only one study”7 is somewhat demonstrably randomized. The dynamic balance technique known as “minimization” used by Weiger et al.9,10 is a widely accepted randomization technique. In March 2000, we consecutively subjects were alternately allocated to 1- or 2-visit treatment. All 3 studies were prospective in design, and none could be construed to be biased in patient allocation to a particular treatment protocol.

4. The “vastly different criteria” for outcome assessments among the 3 papers were in fact all based on healing of apical periodontitis as assessed by clinical and radiographic criteria. One study used the PAI for radiographic assessment while the other 2 used conventional criteria. “Vastly different”??? Importantly, all studies applied the same criteria to both treatment groups within the study.

5. The statement that Trope et al.7 did not use calcium hydroxide as an intracanal medicament in their 2-visit treatment group is incorrect. Their study included 1 multi-visit group with and 1 without an intracanal medicament. Our analysis included only the group medicated with calcium hydroxide.

6. We are puzzled by the statement that sample size in both component studies as well as the final cohort “are all too small for the conclusions that there was no significant difference between 1- or 2-visit treatment protocols.” A statistically significant level of difference is achievable regardless of sample size.

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above a certain minimum, depending on the magnitude of the difference between groups; conversely, lack of significance can occur regardless of sample size if the difference is too small. An n of approximately 20 per group (as in 2 of the included studies) or 67 to 79 per group (in the pooled data) is more than sufficient to demonstrate statistical significance or its absence, depending on the difference. The real issue—whether lack of statistical significance means that there is genuinely no difference in healing or whether the sample size is too small to demonstrate a small difference if it existed—was addressed in considerable detail in our Discussion.

7. The risk that less informed readers will draw “erroneous conclusions” is largely beyond our control. Our role is to assess current information on the extent of available evidence, the strength of that evidence, and the conclusions that can reasonably be drawn from the evidence. All of these have been clearly addressed in the paper, including explicit statements such as “only 3 RCTs were identified”; “the level of evidence is weak”; “the difference in healing rate between these 2 treatment regimens was not statistically significant.” The only possible alternative conclusion to be drawn from the available evidence (unless we have overlooked any relevant papers) is that there is insufficient evidence to draw any conclusion. That would require a denial of the outcomes of 3 peer-reviewed prospective studies by highly respected endodontists.

Discerning readers may wish to contrast your comments with a more rigorous analysis of our paper.

The need for good clinical studies in endodontics, and for their careful analysis and interpretation, is great. As editor of 1 of 3 leading endodontic journals, you have the opportunity, indeed the obligation, to promote the highest standards of clinical research. The International Endodontic Journal committed itself 3 years ago to requiring conformity to CONSORT guidelines for clinical studies reported in the journal. Oral Surgery Oral Medicine Oral Pathology Oral Radiology Endodontics could do the same. Experts could be invited to provide definitive guidelines for future clinical studies in relation to particular topics of interest, with the guidelines published in Oral Surgery Oral Medicine Oral Pathology Oral Radiology Endodontics. Endodontics would benefit enormously from such positive leadership.

Chanhrit Sathorn, DDS, GradDipClinDent, DClinDent
Peter Parashos, BDS, MDSc, PhD
Harold Messer, BDS, MSc, PhD

Endodontic Unit
School of Dental Science
The University of Melbourne
Carlton Victoria, Australia

REFERENCES

doi:10.1016/j.ajr.2007.06.007

In reply:

To Drs. Sathorn, Parashos, and Messer

I am glad that my editorial was thought-provoking, because thinking often helps in arriving at a better understanding of issues at hand.

I first notice that you like to assign some of the responsibility for my concerns about endodontic meta-analysis on editors and reviewers. I gladly take the responsibility for my errors of judgment, but I cannot believe that you, as scientists, accept all printed material at face value. Even publications by “highly respected endodontists” must not be beyond careful critical analysis. Therefore, it is reasonable to expect that the authors of a meta-analysis are predominantly responsible for the content.
You state that “the risk that less-informed readers will draw erroneous conclusions is largely beyond our control.” You may have suggested, in the discussion, that your study has some limitations, but this is not clear when reading your conclusion. It states, “Based on the current best available evidence, single-visit root canal treatment appeared to be slightly more effective than multiple-visit, i.e., 6.3% higher healing rate.” If that statement is not conclusive and under your total control, I don’t know what is conclusive. At the end of your paper, the clinical recommendation based on results states, “In terms of therapeutic efficacy, current best available evidence failed to demonstrate a difference between the 2 treatment regimens.” The fact is that you have not demonstrated anything of the kind.

My comment on narrow inclusion criteria was not to be interpreted as stating that there were more studies to review, but rather that there are too few, if any, qualifying studies on which to base such meta-analysis. Often, when performing searches for studies to include in systematic reviews, the criteria become more important than the quality of the studies unearthed. It is too common for most reviews to verbally and uncritically report findings without carefully assessing the relevance and quality of reports. This is especially important for systematic reviews serving as the foundation for a meta-analysis. It is the responsibility of the author of such a review to be fully knowledgeable and cognizant of the strength and pitfalls of the subject material. I believe that this was not true for the analysis you performed. My comment does not minimize the contribution to the literature by the 3 studies included in your analysis. However, these studies are much too different to allow a compilation of data and summary in a meta-analysis.

Despite your claim that the 3 studies used for the analysis were comparable and acceptable for a meta-analysis, I still believe there are many differences that are not controlled for. There are many factors, some more important than others, affecting the outcome of endodontic treatment. Such factors must be part of inclusion and exclusion criteria before combining outcome studies to enhance total number of cases.

There is certainly a need to control for instrumentation techniques, quality of root canal filling, tooth type, quality of asepsis, and disinfection protocols, just to mention a few.

The criteria for assessment of treatment success and failure were different and not very stringent. One study appears to use the classic Strindberg criteria for success, which is commendable. There is some real inconsistency, however, in that the criteria described as “unchanged” lesion is considered to be “incomplete healing,” and “persisting lesion” is considered to be a “failure.” “Unchanged” and “persisting” are similar judgments although placed in 2 outcome categories. That study also includes numerous multirooted teeth where outcome is less well defined. What might be lost from this study is the reported failure rate, which was hidden in a fog of statistics. The one-visit group had an outright 8% rate of failure, whereas the 2-visit group only had a 3% failure rate. The failure rate is important for the patient because it often requires further treatment. Healed and healing/uncertain cases are often less consequential to the patient.

The second study used an outcome measurement system known as PAI scores. The PAI score is an image-based system which actually has a very limited basis for being accurate. It was introduced in 1986 for outcome assessments and the basis for the scores is extrapolated, with statistical calculations, from cadaver material of human maxillary incisors reported in 1 single publication. There is no other objective study available supporting these results. The PAI score does not identify a clear distinction between presence and absence of a bone lesion which is the hallmark of the Strindberg criteria. Furthermore, there is no documentation available that it may be applicable to any teeth other than maxillary incisors. The problem with the PAI score can be demonstrated by the data presented in one of the discussed studies, where 102 teeth initially were diagnosed with “radiographically demonstrable apical periodontitis.” However, reassessment at the end of the study resulted in 68 teeth with a PAI score of 3 or above (diseased). Thus, the PAI score ostensibly describes lesion size on a sliding scale, but does not provide a clear indication of disease resolution.

Peters and Wesselink used a third system to assess outcome. They combined a system allocating probability for the presence of a periapical lesion with modified Strindberg criteria. They reported no true failures, because a fractured root has absolutely nothing to do with the question investigated. There were 4 cases with decreasing lesion size (score B) in each group. Using the statistical process for outcome assessment used by Weiger et al., the success rate in that study is 100%. Yet, when using the raw data, the teeth with complete periapical healing were 17 of 21 (81%) and 12 of 17 (71%). These disparate success rates (100% vs. 71% and 81%) illustrate the variability between different measurement systems.

I believe there is ample evidence that the 3 studies selected were not truly randomized. When undertaking a study of treatment where every procedural step may be of importance for the outcome, objective randomization is essential. Thus, in studies of the type included in the analysis, randomization must not be done until all instrumentation, irrigation, and other treatment steps
are concluded. At that point randomization can take place, allocating some teeth to immediate root canal filling and other to intracanal dressing and temporization. This would preclude treatment bias which may otherwise be introduced. In one study, it is stated that “every second patient was assigned to group 2.” Despite this effort, group 1 ended up with 21 cases and group 2 had 18 cases. Because “all patients returned for follow-up” it appears that the randomization process was not well controlled.

Trope et al. used pretreatment randomization. Despite this, the 3 experimental groups ended up with 31, 26, and 45 cases. This was later adjusted to adapt for the PARI scoring.

In the third study, “minimization” was used as a substitute for formal randomization. This method is often a preferred and widely acceptable alternative ensuring balance between groups for several prognostic factors, even in small samples. The treatment allocated to the next participant enrolled in the trial depends on the characteristics of participants already enrolled. This is an attempt to minimize imbalances between multiple factors that may affect outcome. For greatest objectivity in the process, software may be used. There is little evidence, however, that the minimization attempts worked. Thus, cases have not been evenly distributed between tooth groups, number of root canals, symptoms, and pretreatment coronal restorations. Based on these comments, I believe that the 3 studies used as basis for the meta-analysis were not randomized studies.

You correctly state that your “role is to assess current information on the extent of available evidence, the strength of that evidence, and the conclusions that can reasonably be drawn from the evidence.” It is questionable whether you have achieved your stated objective. It is not enough to simply test for the strength of evidence by statistics alone. All factors of relevance, such as clinical and microbiologic aspects, must be critically appraised before statistical assessment. The onus remains with you to recognize the limitations and variations between the studies before reaching your conclusions.

Conformity to CONSORT guidelines is a decision made by the Editor-in-Chief. The Endodontology section does not independently make such a decision. Even if such conformity is declared by the journal, it is still up to the individual reviewer and editor to control this process. There are many examples that despite conformity declaration by a journal this process does not always work flawlessly.

In conclusion, I still believe that at this time there are not sufficient numbers of strictly controlled studies in the endodontic literature to use as basis for meaningful meta-analysis. The focus should be on undertaking such controlled studies and not dilute our efforts on rather meaningless meta-analysis of insufficient data.

Latz S. W. Spangberg, DDS, PhD
Section Editor, Endodontology

REFERENCES

doi:10.1016/j.tripleo.2007.06.008
LETTERS TO THE EDITOR

Save the baby

To the Editor:

If one measure of a good editorial is its ability to capture the reader's attention, then the recent editorial by Dr. Lars Spangberg is very good indeed. I agree with many aspects of his editorial, including the key point that a systematic review is an important tool that collects, evaluates, and integrates a body of research addressing an important question of interest.

Unfortunately, many of the statements in the editorial do not match the current applications of this robust tool in biomedical research. For example, an important systematic review on bisphosphonate-associated osteonecrosis has been recently published. Should this review also be considered "garbage in—garbage out" simply because the patients were not subjected to randomized controlled trials in a context that clearly would have been unethical? In addition, this research tool has been applied to preclinical research investigating important topics related to biocompatibility of titanium implants, spinal cord ischemia, arrhythmias, vasodilation, and so forth. As a clinical scientist who conducts basic research, I must suggest that scientists also find value when systematic reviews are applied to the preclinical literature. Moreover, clinical recommendations for many analgesics are based upon systematic reviews integrating a common clinical outcome (pain) from patients having disparate clinical procedures including third molar extraction, tonsillectomy, epistomy, and general surgery. Indeed, some systematic reviews are based on only one evaluable clinical study. Let us wonder about technical quality, the last 2 cited studies were Cochrane Reviews.

From this broader context of how biomedical research uses this important tool, one wonders whether comparatively small differences in clinical protocols are sufficient to completely discard a carefully conducted systematic review of endodontic outcomes. Indeed, potentially important clinical insights are lost when one discards systematic reviews. For example, if calcium hydroxide does not predict endodontic outcome, then perhaps other factors should be evaluated in prospective clinical trials. In addition, one wonders whether systematic reviews of endodontic in vitro studies are de facto suspect, when this tool has proven useful in other fields of preclinical research.

While it is certainly true that systematic reviews have a major impact when integrating numerous high-quality randomized controlled trials, it must be appreciated that this is not an exclusive application for this research tool.

Systematic reviews are like any other tool in biomedical research. They have considerable power in integrating the literature and have particularly favorable applications in the evaluation of clinical research. However, like any other research method, proper interpretation is needed. In contrast to a view of "GIGO," I am more concerned about throwing the baby out with the bathwater.

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REFERENCES


doi:10.1016/j.tripleo.2007.07.036

In reply:

Dear Dr. Hargreaves,

I looked for the baby but could not find it.

Lars, S. W. Spangberg
Editor, Endodontology Section
Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology, and Endodontics

doi:10.1016/j.tripleo.2007.07.035
Single-visit more effective than multiple-visit root canal treatment?

When individuals undergo root canal treatment for apical periodontitis, does single-visit treatment result in a lower healing (success) rate than multiple-visit treatment?


Data sources Literature was searched using the Cochrane Controlled Trials Register (CENTRAL), Medline, Embase and HealthStar databases. Reference lists from identified articles were scanned and a further search made using names of authors of the identified articles. Papers that had cited these publications were also identified through the Science Citation Index to identify potentially relevant subsequent primary research.

Study selection Two reviewers scanned all titles and abstracts. Articles were included if subjects had a no relevant medical history; subjects presented with mature teeth with infected necrotic root canals and radiographic evidence of periapical bone loss (as an indication of preoperative canal infection), all selected root canals had not received any endodontic treatment previously, patients underwent non-surgical root canal treatment during the study, and the number of teeth showing radiographic evidence of healing was the outcome measure.

Data extraction and synthesis Data were abstracted by two reviewers. The principal measure of treatment effect was risk difference with the fixed-effect method for combining study estimates being used to produce an overall estimate. Between-study heterogeneity was assessed using standard $p^2$ test or Q-statistic.

Results Only three randomised controlled trials (RCT) were identified and included in the review, covering a total of 146 cases. Sample size of all three studies was small. None demonstrated a statistically significant difference in healing rates. Risk differences (RD) of included studies were combined using the inverse variance-weighted method (pooled RD, −6.3%; 95% confidence intervals, −20.3 to +7.8).

Conclusions Based on the current best available evidence, single-visit root canal treatment appears to be slightly more effective than multiple visits, that is, it had a 6.3% higher healing rate. The difference in healing rate between these two treatment regimens was not statistically significant ($p=0.3809$, however).

Commentary A major goal of nonsurgical root canal treatment (NSRCT) is the prevention or treatment of apical periodontitis, leading to the preservation of natural teeth. Three major factors affect the healing of apical periodontitis. First, therapeutic factors such as different regimens of NSRCT or the quality of subsequent restorations are thought to be critical in treatment outcomes. Second, host factors such as diabetes and, possibly, smoking have been associated with a decreased response to treatment. Third, microbial factors, such as the presence of Enterococcus faecalis, are associated with cases having a poor clinical outcome.

There is considerable interest in the efficacy of different regimens of NSRCT on the healing of apical periodontitis, largely because the treatment protocol is under the clinician's control. Thus, this study by Sathorn and co-workers is of particular importance because it compares a one-visit treatment protocol with a multiple-visit treatment regimen that included interappointment treatment with calcium hydroxide. This intervention is based upon sound biological principles, the well-recognised antimicrobial properties of calcium hydroxide against root, but not all, endodontic microflora.

The study is a well-designed systematic review and the authors carefully identify potential design issues and limitations to the work. Unfortunately, only three RCTs were identified, leading to a relatively small total sample size. In addition, these studies provide some but not all information about other relevant factors (e.g., quality of subsequent restorations, patient history of diabetes).

Given these limitations, the study does provide an important conclusion: there was no significant difference in the healing of apical periodontitis in the one-visit cases versus the multiple-visit cases with calcium hydroxide treatment. Indeed, if anything, one-visit treatment tends to have a better outcome.

These results have strong therapeutic and research implications. First, the finding of this systematic review that multiple visits with calcium hydroxide treatment does not improve upon clinical outcome provides at least a minimal level of evidence for reconsidering one versus two appointments when planning NSRCT procedures. Although it would be optimal to base clinical recommendations upon a larger body of RCT, the authors correctly note that it is very unlikely that subsequent research would result in a greater than 10% improvement with multiple-appointment treatment. This is based upon the observation that the present study's 95% confidence interval ranges from −7.9% (i.e., favouring multiple appointments) to +20.3% (i.e., favouring the single appointment).

Secondly, this finding has considerable scientific implications. In particular, what other NSRCT regimens might further increase success in the healing of apical periodontitis? Current clinical evidence is consistent with a statistically significant but clinically small (≈10%) difference in instrumentation/obturation methods. In addition, the quality of the coronal restoration or the post and core appear to have a significant and perhaps larger impact on clinical outcomes. These initial studies need to be repeated by other RCT with subsequent systematic reviews.
ENDODONTICS

Finally, the biological mechanisms for persistent apical periodontitis should be studied from the perspective of developing new treatment approaches to further improve upon the success in treating this disease.

Practice point

● The review shows that multiple visits with calcium hydroxide treatment does not improve upon clinical outcome and provides at least a minimal level of evidence for considering one versus two appointments when planning NSRCT procedures.

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Author/s:
SATHORN, CHANKHRIT

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Effectiveness and efficiency: systematic reflections on single- and multiple-visit root canal treatment

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