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Single- or multiple visit root-canal treatment: Systematic Review, Meta-Analysis and Trial Sequential Analysis

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Abstract

Objectives: Single-visit root-canal treatment has some advantages over conventional multi-visit treatment, but might increase the risk of complications. This systematic review compared both treatments in permanent teeth.

Data: Controlled trials comparing single- versus multiple-visit root-canal treatment of permanent teeth were included. Trials needed to assess risk of long-term complications (pain, infection, new/persisting/increasing peri-apical lesions ≥1 year after treatment), risks of short-term pain, risk of flare-up (severe pain or swelling after commencement or continuation of root-canal treatment).

Sources: Electronic Databases (PubMed, Embase, Cochrane Central) were screened, random-effects meta-analyses performed, and trial sequential analysis used to control for risk of random errors. Evidence was graded according to GRADE.

Study selection: 29 trials (4341 patients) were included, all but six showing high risk of bias. Based on ten trials (1257 teeth), risk of complications was not significantly different in single- versus multiple-visit treatment (RR: 1.00 [95% CI: 0.75/1.35]; weak evidence). Based on twenty studies (3008 teeth), risk of pain did not significantly differ between treatments (RR: 0.99 [95% CI: 0.76/1.30]; moderate evidence). Risk of flare-up was recorded by eight studies (1110 teeth) and was significantly higher after single- versus multiple-visit treatment (RR: 2.13 [95% CI: 1.16/3.89]; very weak evidence).

Conclusions: According to trial sequential analysis, firm evidence for benefit, harm or futility was not reached for any of the outcomes.

Clinical significance: Dentists can provide root-canal treatment in one or multiple visits. Given the possibly increased risk of flare-ups, multiple-visit treatment might be preferred for certain teeth (e.g. those with peri-apical lesions).

Strength and limitations of this study

- Full protocoll published on PROSPERO (CRD42016036386)
- Quantitative strength of evidence was assessed by Trial Sequential Analysis
- Findings are supported by moderate to weak evidence according to GRADE

Introduction

After root-canal treatment, teeth can experience short- and/or long-term complications. Short-term complications include postoperative inflammation of peri-apical tissues leading to mild pain, or flare-up (i.e. an acute exacerbation of pulpal or peri-apical pathosis after root-canal treatment, like severe unbearable pain and swelling). Pain and swelling have been associated with instrumentation or irrigation transporting medications, infected debris and bacteria into the peri-apical tissues. Inadequate instrumentation and disinfection lead to bacterial persistence within the root-canals and consequent (re)contamination of peri-apical tissue [1 2]. Long-term outcomes include persisting inflammation and infection, resulting in abscess, sinus track formation, radiographic signs of peri-apical bone resorption or severe pain, with subsequent need to endodontically re-treat or remove teeth [3 4]. Both short and long-term outcomes seem to be affected by the preoperative condition of the tooth (tooth type, vitality, symptoms, peri-apical conditions) [4]. Moreover, they might be affected by how root-canal treatments are provided.

Single-visit root-canal treatment attempts instrumentation, disinfection and obturation of the root-canal system in one visit. In contrast, multiple-visit root-canal treatment performs the instrumentation (or large parts of it) in the first and the obturation in the second visit, while the disinfection is provided in both visits via irrigation. Moreover, a disinfecting medication is placed in the canals between visits to allow further reduction of bacterial numbers. While single-visit treatment has obvious advantages over conventional multiple-visit treatment (like reduced number of visits, no need for repeated application of anesthetics or rubberdam, no intermediary restoration), it might be disadvantageous both with regards to short and long term outcomes.

A number of reviews have compared single- versus multiple visit root-canal treatment [3 5-8]. Some of these are outdated [3 6], others investigate only short-term pain as outcome [5], again others build on evidence beyond controlled trials like cohort studies or expert opinions

[7], or pooled short- and long-term outcomes, which does not allow to weigh them against each other [8]. The present review aimed to comprehensively compare the currently available controlled trial data on short- and long-term complications of single- versus multiple visit root-canal treatment. Our primary objective was to answer the question: In patients needing root-canal treatment, is single-visit treatment significantly more effective than multiple visit treatment with regards to risk of long-term failure? The secondary objective was to compare both treatments with regards to risk of short-term postoperative pain as well as the risk of flare-up. We further investigated moderators of risks using subgroup or meta-regression analysis, and assessed how statistically robust current evidence is with regards to type I or II errors using trial sequential analysis. The review should guide the conduct of further studies and help to deduct clinical recommendations.

Methods

Eligibility criteria

This systematic review (registered at PROSPERO CRD42016036386) included trials that

- were randomized controlled trials or controlled trials without signs of selection bias (i.e. treatments were not allocated according to preoperative tooth status etc.). Sensitivity analyses were performed to account for the introduced risk of bias in case of treatment allocation not being at random.
- compared single-visit with multiple visit root-canal treatment in permanent teeth with closed apices and without internal resorption, regardless of the pre-operative condition (meta-regression and subgroup analyses were performed to account for different conditions).
- reported on risk of long-term complications (≥1 year after treatment), and/or risk of experiencing any short-term pain, and/or risk of short-term flare-up.

Outcomes

The primary outcome was risk of long-term complications, defined as pain, infection/swelling/sinus track formation, or development, persistence or aggravation of peri-apical lesions or widening of the periodontal ligament etc. ≥1 year after treatment. No standard as to how peri-apical lesions needed to be assessed or categorized was set, as a range of classification systems are currently used [3].

The secondary outcomes were

- risks of experiencing any short-term pain (<1 year after treatment) after obturation or after instrumentation or after both. To detect the largest difference between treatments, pain was extracted at the shortest recording time point after treatment. As we did not separate mild, moderate or severe pain, and even included outcome measures like having taken any pain medication in this outcome, risk of any pain does not necessarily indicate a further treatment being required.
- risks of experiencing short-term flare-up, usually defined as an acute exacerbation of an existing asymptomatic pulpal or peri-apical pathosis. Note that flare-up was not defined consistently across studies; some studies reported flare-up whilst having treated both symptomatic and asymptomatic teeth. We therefore defined flare-up as a short-term symptoms (<1 year, usually directly after commencement or conclusion of root-canal treatment) which led or can be assumed to lead to a further intervention (like reaccessing/reinstrumenting an incompleted treatment; completing an incision and drainage procedure, or reperforming root-canal treatment).

Searches

We have searched Medline via PubMed, Embase via Ovid and Cochrane Central. Moreover, opengrey.eu was searched to identify accepted, but not published studies. In addition, reference lists of identified full-texts were screened and cross-referenced. We contacted study authors if required to obtain full-texts. Neither authors nor journals were blinded to reviewers. No language restriction was set.

The applied search strategy can be found in Fig. 1.

Study records

Data management

A piloted spreadsheet was used for data extraction and management.

Selection process

Two reviewers (FS, GG) independently screened titles and then compared their findings. In case of disagreement, titles were included to obtain full texts. Full texts were assessed independently after de-duplication. Studies were included after agreement with consensus in cases of disagreement being reached through discussion.

Data collection process

Data extraction was performed independently by two reviewers (FS, GG). Disagreements were resolved through discussion.

Data items

The following items were collected: Author names, year, sample, setting, tooth type, pulp vitality, preoperative pain, presence of radiographically detectable periapical lesions, instrumentation type, obturation type, irrigation, medication, intermediate restoration, no of visits, evaluation method, findings.

Outcomes

Outcomes and outcome measures were extracted. For studies reporting non-significant findings without any further information, this was extracted to allow including these into a sensitivity meta-analysis (see below).

Data synthesis

Meta-analysis

The statistical unit was the tooth. Clustering was near absent in most studies. Therefore, the risk of this approach leading to artificially narrow confidence intervals is low [9]. A continuity correction of +1 was performed in case of zero events. Random-effects meta-analysis using the DerSimonian-Laird estimator of variance was performed using Comprehensive Meta-Analysis 2.2.64 (Biostat, Englewood, NJ, USA), with Risk Ratios (RR) and 95% confidence intervals (95% CI) as effect estimates. Fixed effect models were used as well, but did not yield significantly different findings given the low level of heterogeneity. Unit-of analysis issues were handled as described in the appendix. Heterogeneity was assessed using Cochran's Q and I^2-statistics [10]. Funnel plot analysis and Egger test were performed to assess small study effects or publication bias [11 12]. RR were adjusted (RRa) to check the impact of possible publication bias [13].

Subgroup and meta-regression analyses

Subgroup and meta-regression analyses were carried out to assess the impact of a root-canal medication being used (or not) in multiple-visit treatment, pulp vitality prior treatment, preoperative pain, and the presence of radiographically detectable peri-apical lesions on effect estimates. Details can be found in the appendix.

Confidence in data

Risk of bias was assessed and classified according to Cochrane guidelines [12]. Note that we did not assess performance bias (blinding of operators), as this is not feasible in trials comparing single- versus multiple-visit treatment.

In addition, trial sequential analysis (TSA) was performed to assess if quantitative findings are robust, and to calculate the required information size (RIS), i.e. the cumulative sample size needed to yield significant differences between treatments [14 15]. RIS is then adjusted for heterogeneity/diversity (DARIS). TSA additionally estimates trial sequential monitoring

boundaries (TSMB), i.e. statistical thresholds for significance which are adapted depending on the so far reached sample size. Firm evidence is assumed to be reached when the Z-curve crosses the TSMB for benefit or harm before the DARIS was reached. Effect estimates supported by only few small trials are handled stricter than those supported by large samples. In addition to such superiority/inferiority TSMBs, monitoring boundaries for futility were calculated. These indicate if further trial conduct is likely to be futile, i.e. if sufficient evidence has been accrued to claim non-inferiority of treatments (which would be most relevant for this review). Further details have been reported elsewhere [16] and can also be found in the appendix.

Evidence for each outcome effect estimate was graded according to the GRADE working group of evidence [17] using Grade Profiler 3.6, and strength of recommendations deducted accordingly [18].

Results

Results of the searches

From 817 records, 64 were screened full-text. After cross-referencing 67 articles were screened and 29 included (Tab. 1). Excluded studies and reasons for exclusion can be found in the appendix (Tab. S1).

Overall, 4341 (mainly adult) patients had been treated (Tab. 1). Six trials treated only teeth with vital pulps, six treated vital and non-vital teeth or did not specify vitality; the remaining trials treated non-vital teeth. Three trials clearly stated to treat only teeth with preoperative pain, 15 treated both painful and painless teeth or did not state any details on preoperative symptoms, the remaining trials treated only teeth without preoperative symptoms. Ten trials included only teeth with peri-apical lesions, 13 trials did not report on radiographic status of the peri-apex or treated both teeth with and without lesions; the remaining trials treated only teeth without any detectable lesions.

Six trials were found to have low risk of bias (Tab. S2), the remaining trials showed high or unclear overall risk of bias. This was mainly due to lack of examiner blinding or allocation concealment. Two trials did not at all report on randomization, and were treated accordingly in meta-analysis. The majority of trials mentioned randomization, but not how sequences were generated. Attrition was generally limited (as most trials did only assess short-term pain, see below), as was risk of selective reporting.

Risk of long-term complications

Long-term complications were investigated by ten trials, with a total of 1257 teeth being treated. Mean follow-up was 2.3 years (range: 1-5 years). All trials had used calcium hydroxide as medication in the multiple-visit group. All but two trials had high risk of bias. Risk of complications was not significantly different in single- versus multiple-visit treatment (RR: 1.00 [95% CI: 0.75/1.35]). Heterogeneity was low. Publication bias not detected via Egger's test (p=0.36) or funnel plot analysis (Fig. 2a, Appendix Fig. S1a).

Preoperative conditions were not found to significantly impact on effect estimates (Tab. 2). Studies which did not state to have randomly allocated treatments did not find significantly different risk ratios (p=0.35). Using TSA, we found neither the conventional thresholds for benefit or harm nor the TSMB for benefit, harm or futility to be reached. Sample size was far below DARIS (Fig. 2b). Given that risk of bias was serious and the number of events low (leading to imprecision), our confidence in this finding was weak.

Risk of experiencing any postoperative pain

20 studies used binary estimates to express risk of short-term pain. Of these, three had used a factorial design, with resulting subgroups being handled as independent studies. Three further studies used visual-analogue scales and reported pain to not be significantly different; these were included in a sensitivity analyses. For the base-case analysis, a total of 3008 teeth were available and assessed. Pain had been recorded after a mean 2 days

(range: 1-7) postoperatively. Three trials had compared pain only after instrumentation, the other studies compared pain after obturation. All but three trials showed high risk of bias.

Risk of pain was not significantly different in single- versus multiple-visit treatment (RR: 0.99 [95% CI: 0.76/1.30]). Heterogeneity was moderate. There was no indication for publication bias via Egger's test (p=0.46) or funnel plot analysis (Fig. 3a, Appendix Fig. S1b). Preoperative conditions or the use of a calcium hydroxide instead of no root-canal medication between visits had no significant impact on effect estimates (Tab. 2). Studies which did not state to have randomly allocated treatments did not find significantly different risk ratios (p=0.46). Including imputed studies which had only reported differences between groups to be non-significant (but not given an effect estimate) increased the total number of assessed teeth to 3417, but did not significantly change our estimates (RR=1.00 [0.86/1.21]). Excluding those trials which only reported on pain after instrumentation, not obturation, also had no significant impact (RR=0.99 [0.84/1.17]). Using TSA, we found the conventional thresholds for benefit to be spuriously crossed, while the TSMB for benefit was not reached. Futility boundaries were not constructible due to too few data being available. The sample size was far below DARIS (Fig. 3b). Given the serious risk of bias, but only limited evidence for imprecision, this finding is supported by moderate evidence according to GRADE.

Risk of flare-up

Risk of flare-up was recorded by eight studies. A total of 1110 teeth had been followed over a period of 7-10 days. All studies stated to be randomized trials, two studies showed low, the rest high risk of bias.

Risk of flare-up was significantly higher after single- versus multiple-visit treatment (RR: 2.13 [95% CI: 1.16/3.89]). Heterogeneity was low. There was some indication for publication bias based on funnel plot analysis, but not Egger's test (p=0.26). Adjusting the estimate accordingly increased the RR (Fig. 3a, Appendix Fig. S1c). Preoperative conditions and the root-canal medication had no significant impact on effect estimates (Tab. 2). Using TSA, we

found the conventional thresholds for harm to be spuriously crossed, while the TSMB for harm was not reached. Futility boundaries were not constructible due to too few data being available. The sample size was far below DARIS (Fig. 3b). Given the serious risk of bias, imprecision and publication bias being present, our confidence in this finding is supported by only very weak evidence according to GRADE.

Discussion

Even after optimal root-canal disinfection via instrumentation and irrigation, bacteria usually remain within the root-canal system [19 20]. During multiple-visit root-canal treatment, an antibacterial medication like calcium hydroxide is placed in the root-canals, thereby aiming to further disinfect the canals between treatment appointments, the efficacy of which remains unclear at present [19 21-23]. In contrast, in single-visit root-canal treatment any further appointments and intra-canal medications are omitted, and the root-canal system iobturated directly after instrumentation and irrigation, aiming to seal remaining bacteria and deprive them from both space and nutrition [3 24-26].

We found single-visit treatment to not increase risk of long-term complications. This was our primary outcome, as such complications oftentimes decide the fate of the tooth [27-29]. It is noteworthy that this was supported by a range of studies (i.e. studies with high or low risk, small or large samples, in adults or adolescents, vital or non-vital teeth, teeth with or without peri-apical lesions) with relatively homogenous findings. Only one trial [30] found significant differences between groups (favoring single-visit treatment), all others did not find one treatment superior over the other.

Based on our analyses, the discussed confounders do not seem to significantly affect the relative risk of complications. Even in teeth with peri-apical lesions, single-visit treatment showed no significantly different risk of complications. This finding is in line with that from a previous review [6]. We want to highlight that our performed meta-regression and subgroup

analyses are potentially underpowered, with high risk of type II errors. In general, our findings on the risk of complications outcome are supported by limited data, as indicated by TSA. Based on this analysis, no firm evidence on benefit, harm or futility is available (while the cumulative Z-curve never crosses any threshold for significance, once more confirming a trend towards non-difference of treatments).

The resulting evidence was graded as weak, mainly due to risk of bias of trials. Thus, a number of recommendations towards future studies need to be made: First, future trials should have higher internal validity, e.g. by performing and reporting on sequence generation, by sufficiently concealing the allocation, and by blinding assessors, all to reduce the risk of selection and detection bias. We are well aware that blinding operators or patients is impossible in such trials; future reviews should reflect on this when assessing risk of bias (as we did accordingly). Second, trials should be performed in realistic (primary care) settings with sufficiently long follow-up periods, as complications are expected to occur long-term. Third, trials should aim to investigate the relevance of preoperative conditions as possible confounders, as current data are insufficient to conclude on the suitability of single- versus multiple-visit treatment in different teeth or patients.

We also found single-visit treatment to not significantly increase the risk of short-term postoperative pain, which is in line with findings from previous reviews [3 6 31]. Pain is a relevant outcome, despite being reported only for brief periods after treatment and not being a strong predictor for success [20], as it is directly burdening patients and could influence their attitude and behavior towards future endodontic treatment. Our findings were again relatively consistent between trials regardless of their risk of bias, setting, patients or treated teeth. Only three studies found significant differences between groups; two in favor of single-visit treatment [32 33], one in favor of multiple-visit treatment [34]. All three were performed in non-vital teeth. It is again important to note that while we did not identify significant confounders (which is in line with previous findings) [35], our meta-regression analyses are (as discussed) of limited power. However, the overall number of treated teeth was relatively

high, and while currently, data was insufficient to establish firm evidence, we expect futility boundaries of TSA to be reached if future trials confirm these findings. Given the discussed uncertainties associated with the preoperative condition (vitality, symptoms), researchers should account for these confounders when designing and evaluating future trials in the field.

We found single-visit treatment to significantly increase the risk of flare-up, which is in agreement with a previously identified increased risk of swelling after single-visit treatment [3]. It should be highlighted our analysis for this outcome built on only few, mainly high risk trials, and that one particular study [36] contributed a lot to the effect estimate given its weighting. This weighting was the result of the high incidence of flare-up in this study (20% in the single-visit group), which is much higher than that in all other trials. Excluding this study from the analysis decreased the effect estimates, with no significant difference between groups remaining (RR: 1.85 [0.89/3.86]). Given that TSA indicated that no firm evidence has been reached so far, caution is thus required when interpreting our finding regarding flare-up.

This review has a number of limitations. First, it builds only on randomized or at least controlled trials. While we see the value of practice-based long-term cohort studies (which have higher external validity and yield findings in a more relevant timeframe), we actively restricted our review on controlled studies to minimize the risk of selection bias, the impact of which can be expected to be potentially severe given that treatment decisions might be made based on the preoperative condition of the tooth. For example, dentists might be more willing to perform single-visit treatment in vital teeth, or molars might be treated in multiple visits more often due to practical reasons. This would greatly distort the true relative efficacy of both therapies.

Second, our primary outcome, complications, is a composite of different components like long-term pain, clinical signs of inflammation and infection (swelling, sinus track formation),

and radiographic success (which does not need the patient to experience symptoms). For each component, a decision to re-treat or not might differ depending on who is deciding: Dentists (and researchers specializing in endodontics) might see a persistent peri-apical lesion as an indication to re-treat even in the absence of symptoms (anticipating such symptoms to occur at some stage in the future, with poorer prognosis for re-treatments). In contrast, patients might not be willing to re-treat such tooth (which might as well be justified when considering the success rates of the available re-treatments and the resulting treatment costs) [29].

Third, one of our secondary outcomes, the risk of experiencing any postoperative pain, does not account for the degree of pain, losing a significant amount of information. That was done, a most trials reported pain using either a binary scales (pain yes/no) or ordinal scales, which did not always use identical categories and pose great difficulties when pooling them (or require the definition of a certain pain threshold, which is usually arbitrary). Future studies should use continuous outcome measures like visual analogues scales, allowing to fully display the recorded information on pain. It is noteworthy that those studies which used such scales also found no significant difference of pain levels between treatments.

Last, most included trials reported only on very limited periods after treatment. While this might be acceptable for short-term pain, a follow-up of mean 2.3 years is insufficient to truly reflect “long-term” complications. This is closely related with the discussed limitations of randomized trials, which are seldom able to follow-up teeth for much longer given the high associated efforts and costs.

In conclusion and within the limitations of this review, dentists can provide root-canal treatment in one or multiple visits. Further recommendations towards when to prefer one treatment over the other are currently not available. Given the possibly increased risk of flare-up, a careful recommendation could be to prefer multiple-visit treatment in teeth where the risk if complication is increased (e.g. teeth with existing peri-apical lesions). Clinical

decisions should be made with practical aspects (like scheduling of patients) and patients' and dentists' preferences in mind.

Tables

Table 1: Included studies.

Study	Patients	Vital/ pain/ lesion	Instr.	Medication	Obtur.	No. of visits	Pain Pain/sample single-visit; Pain/sample multiple-visit; recall	Flare-up Flare-ups/sample single-visit; Flare-ups/sample multiple-visit; recall	Long-term complications Complications/sample single-visit; Complications/sample multiple-visit; recall
Akbar 2013 (37)	100 adults or adolescents	no/ unclear/ yes	hand	calcium hydroxide	lateral	2		5/50; 4/50; 7 days	
Albashaireh & Alnegreshi 1998 (33)	300 adults or adolescents	yes/ no /unclear	hand	none	lateral	2	4/40; 3/36; 1 day		
		no/ no/ no	hand	none	lateral	2	33/102; 55/113; 1 day		
Al-Negrish & Habahbeh 2006 (38)	120 adults or adolescents	yes/ no/ no	hand	calcium hydroxide	lateral	2	8/54; 14/58; 2 days	1/54; 3/58; 7 days	
DiRenzo 2002 (39)	80 adults	both/ yes/ unclear	rotary	none	lateral	2	-/39; -/33; 1 day no significant difference on continuous scale		
Dorsani 2013 (40)	57 adults	no/ unclear/ yes	rotary	calcium hydroxide	lateral	2			10/24; 6/22; 1 year
Fava 1989 (41)	48 adults and children	no/ no/ unclear	hand	phenole	lateral	2	1/30; 0/30; 2 days		
Fava 1994 (42)	52 adults or adolescents	yes/ yes/ unclear	hand	calcium hydroxide	lateral	n.g.	2/30; 1/30; 1 day		
Gesi 2006 (43)	256 adults	yes/ both/ no	hand	calcium hydroxide	lateral	2	16/130; 18/126; 7 days		9/123; 8/121; 3 years
Ghoddusi 2006 (32)	60 adults	no/ both/ yes	hand	calcium hydroxide	lateral	2	1/20; 8/20; 3 days	7/20; 0/20; 3 days	
Ince 2009 (44)	306 adults	yes/ both/ no	hand	none	lateral	2	19/87; 16/66; 3 days		
		no/ both/ mixed	hand	none	lateral	2	9/66; 14/87; 3 days		
Jabeen 2014 (34)	120 adults or adolescents	no/ no/ no	unclear	calcium hydroxide	lateral	2	23/60; 11/60; 1day		
Liu & Leng 2013 (45)	143 adults	no/ unclear/ mixed	unclear	cortisomal	lateral	2-3	52/95; 28/48; 1 day		10/87; 4/42; 1 year
Molander 2007 (46)	94 adults	no/ no/ yes	rotary	calcium hydroxide	lateral	2			17/49; 10/40; 2 years
Mulhern 1982 (47)	60 adults or adolescents	no/ no/ mixed	hand	none	lateral	3	7/30; 6/30; 2 days		
Oginni 2004 (36)	255 adults	both/ both/ mixed	unclear	unclear	lateral	n.g.	58/107; 61/136; 1 day	19/104; 10/123; 7 days	
Paredes-Vieyra 2012 (30)	287 adults	no/ no/ yes	rotary	calcium hydroxide	lateral	2			5/146; 15/136; 2 years
Pekruhn 1981 (48)	102 cases of unclear age	unclear/ unclear/ unclear	hand	formocresol	vertical	2	8/51; 8/51; 1 day		
Penesis 2008 (49)	97 adults	no/ unclear/ yes	rotary	calcium hydroxide+ CHX	vertical	2			7/35; 7/31; 2 years
Peters and Wesslink 2002 (50)	39 adults	no/ no/ yes	hand	calcium hydroxide	lateral	2			0/21; 1/17; 4.5 years
Prashanth 2011 (51)	32 adults	no/ unclear/ yes	rotary	unclear	vertical	2	1/8; 0/8; 2 days		
		yes/ unclear/ no	rotary	unclear	vertical	2	1/8; 1/8; 2 days		

Rao 2014 (52)	148 adults	no/ unclear/ unclear	rotary	none	lateral	2	-/74; -/74 1 day no significant difference on continuous scale		
Risso 2008 (53)	118 adolescents	no/ both/ mixed	hand	calcium hydroxide	lateral	2	-/57;-/61;1 day results not reported	1/57;1/61; 10 days	
Singh and Kargh 2012 (54)	200 adults	both/ unclear/ no	rotary	none	lateral	2	-/94; -/94; 1 day no significant difference on continuous scale	0/9; 0/94; 6 days	
Trope 1999 (55), Waltimo 2005 (56)	81 adults	no/ unclear/ yes	hand	calcium hydroxide	lateral	2			9/45; 6/31; 1 year
Wang 2010 (57)	100 adults	yes/ yes/ no	rotary	calcium hydroxide	lateral	2	28/43; 27/46; 1 day	1/43; 1/46; 7 days	
Weiger 2000 (24)	73 adults or adolescents	no/ both/ yes	hand	calcium hydroxide	lateral	n.g.			3/36; 2/31; up to 5 years
Wong 2015a (58)	567 adults	both/ both/ mixed	rotary	calcium hydroxide	lateral or core carrier	2	68/275; 88/263; 1 day		
Wong 2015b (8)	228 adults	both/ both/ mixed	rotary	calcium hydroxide	core carrier	2-3	25/117; 12/103; 7 days		13/117; 13/103; 2 years
Yoldas 2004 (59)	218 adults	no/ both/ re-treatment	both	calcium hydroxide + CHX	lateral	2	44/106; 32/112; 7 days	8/106; 2/112; 7 days	

Abbreviations: CHX chlorhexidine, n.g. not given, obtur. obturation

Table 2: Meta-regression analysis. LogRR and 95% CI are given to allow comparing relative effect estimates between subgroups of treatments. n: number of studies; n/a not available (as all studies used calcium hydroxide).

	Outcomes		
Subgroups	**Long-term complications (n=10)**	**Any postoperative pain (n=23)**	**Postoperative flare-up (n=8)**
Pain-free versus painful teeth	-0.33 (-1.47/1.14)	0.15 (-0.50/0.80)	1.10 (-2.44/4.63)
Vital versus non-vital teeth	0.10 (-0.90/1.10)	-0.02 (-0.60/0.58)	-0.08 (-2.26/2.10)
Teeth with peri-apical lesions versus teeth without lesions	-0.13 (-1.22/0.98)	-1.18 (-2.91/0.55)	0.79 (-0.87/2.46)
Calcium hydroxide medication versus no medication	n/a	0.11 (-0.27/0.50)	-0.27 (-1.29/0.74)

Contributorship statement

F. Schwendicke, contributed to conception, design, data acquisition, analysis, and interpretation, drafted and critically revised the manuscript; G. Göstemeyer, contributed to conception, design, data acquisition, interpretation and critically revised the manuscript.

Competing interests

The authors declare there is no conflict of interest

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Data sharing statement

No additional data are available.

References

1. Glennon JP, Ng YL, Setchell DJ, et al. Prevalence of and factors affecting postpreparation pain in patients undergoing two-visit root canal treatment. International endodontic journal 2004;**37**(1):29-37
2. Ng YL, Glennon JP, Setchell DJ, et al. Prevalence of and factors affecting post-obturation pain in patients undergoing root canal treatment. International endodontic journal 2004;**37**(6):381-91 doi: 10.1111/j.1365-2591.2004.00820.x[published Online First: Epub Date]|.
3. Figini L, Lodi G, Gorni F, et al. Single versus multiple visits for endodontic treatment of permanent teeth. The Cochrane database of systematic reviews 2007(4):Cd005296 doi: 10.1002/14651858.CD005296.pub2[published Online First: Epub Date]|.
4. Ng YL, Mann V, Rahbaran S, et al. Outcome of primary root canal treatment: systematic review of the literature – Part 2. Influence of clinical factors. International endodontic journal 2008;**41**(1):6-31 doi: 10.1111/j.1365-2591.2007.01323.x[published Online First: Epub Date]|.
5. Raju TB, Seshadri A, Vamsipavani B, et al. Evaluation of pain in single and multi rooted teeth treated in single visit endodontic therapy. Journal of international oral health : JIOH 2014;**6**(1):27-32
6. Su Y, Wang C, Ye L. Healing rate and post-obturation pain of single- versus multiple-visit endodontic treatment for infected root canals: a systematic review. Journal of endodontics 2011;**37**(2):125-32 doi: 10.1016/j.joen.2010.09.005[published Online First: Epub Date]|.
7. De-Deus G, Canabarro A. Strength of recommendation for single-visit root canal treatment: grading the body of the evidence using a patient-centered approach. International endodontic journal 2016 doi: 10.1111/iej.12621[published Online First: Epub Date]|.
8. Wong AW, Tsang CS, Zhang S, et al. Treatment outcomes of single-visit versus multiple-visit non-surgical endodontic therapy: a randomised clinical trial. BMC oral health 2015;**15**(1):162 doi: 10.1186/s12903-015-0148-x[published Online First: Epub Date]|.
9. Masood M, Masood Y, Newton JT. The clustering effects of surfaces within the tooth and teeth within individuals. Journal of dental research 2015;**94**(2):281-8 doi: 10.1177/0022034514559408[published Online First: Epub Date]|.
10. Higgins JPT, Thompson SG. Quantifying heterogeneity in a meta-analysis. Statistics in medicine 2002;**21**(11):1539-58 doi: 10.1002/sim.1186[published Online First: Epub Date]|.
11. Egger M, Smith GD, Schneider M, et al. Bias in meta-analysis detected by a simple, graphical test. BMJ 1997;**315**(7109):629-34 doi: 10.1136/bmj.315.7109.629[published Online First: Epub Date]|.
12. Higgins JPT, Green S, editors. *Cochrane Handbook for Systematic Reviews of Interventions*. Version 5.10 (updated March 2011): The Cochrane Collaboration, 2011.

13. Duval S, Tweedie R. Trim and fill: A simple funnel-plot-based method of testing and adjusting for publication bias in meta-analysis. Biometrics 2000;**56**(2):455-63
14. Wetterslev J, Thorlund K, Brok J, et al. Trial sequential analysis may establish when firm evidence is reached in cumulative meta-analysis. J Clin Epidemiol 2008;**61**(1):64-75 doi: 10.1016/j.jclinepi.2007.03.013[published Online First: Epub Date]|.
15. Thorlund K, Engstrøm J, Wetterslev J, et al. User Manual for Trial Sequential Analysis (TSA). http://www.ctu.dk/tsa/files/tsa_manual.pdf 2011:1-115
16. Schwendicke F, Goestemeyer G, Gluud C. Cavity lining after excavating caries lesions: meta-analysis and trial sequential analysis of randomized clinical trials. Journal of Dentistry 2015;**doi: 10.1016/j.jdent.2015.07.017**
17. Atkins D, Best D, Briss PA, et al. Grading quality of evidence and strength of recommendations. BMJ 2004;**328**(7454):1490
18. Andrews J, Guyatt G, Oxman AD, et al. GRADE guidelines: 14. Going from evidence to recommendations: the significance and presentation of recommendations. J Clin Epidemiol 2013;**66**(7):719-25 doi: 10.1016/j.jclinepi.2012.03.013[published Online First: Epub Date]|.
19. Bystrom A, Sundqvist G. Bacteriologic evaluation of the efficacy of mechanical root canal instrumentation in endodontic therapy. Scandinavian journal of dental research 1981;**89**(4):321-8
20. Sjogren U, Figdor D, Persson S, et al. Influence of infection at the time of root filling on the outcome of endodontic treatment of teeth with apical periodontitis. International endodontic journal 1997;**30**(5):297-306
21. Han GY, Park SH, Yoon TC. Antimicrobial activity of Ca(OH)2 containing pastes with Enterococcus faecalis in vitro. Journal of endodontics 2001;**27**(5):328-32 doi: 10.1097/00004770-200105000-00004[published Online First: Epub Date]|.
22. Siqueira JF, Jr., Lopes HP, de Uzeda M. Recontamination of coronally unsealed root canals medicated with camphorated paramonochlorophenol or calcium hydroxide pastes after saliva challenge. Journal of endodontics 1998;**24**(1):11-4 doi: 10.1016/s0099-2399(98)80204-5[published Online First: Epub Date]|.
23. DiFiore PM, Peters DD, Setterstrom JA, et al. The antibacterial effects of calcium hydroxide apexification pastes on Streptococcus sanguis. Oral surgery, oral medicine, and oral pathology 1983;**55**(1):91-4
24. Weiger R, Rosendahl R, Lost C. Influence of calcium hydroxide intracanal dressings on the prognosis of teeth with endodontically induced periapical lesions. International endodontic journal 2000;**33**(3):219-26
25. Soltanoff W. A comparative study of the single-visit and the multiple-visit edodontic procedure. Journal of endodontics 1978;**4**(9):278-81
26. Oliet S. Single-visit endodontics: a clinical study. Journal of endodontics 1983;**9**(4):147-52 doi: 10.1016/s0099-2399(83)80036-3[published Online First: Epub Date]|.
27. Ng YL, Mann V, Gulabivala K. Outcome of secondary root canal treatment: a systematic review of the literature. International endodontic journal 2008;**41**(12):1026-46 doi: 10.1111/j.1365-2591.2008.01484.x[published Online First: Epub Date]|.
28. Del Fabbro M, Taschieri S, Testori T, et al. Surgical versus non-surgical endodontic re-treatment for periradicular lesions. The Cochrane database of systematic reviews 2007(3):Cd005511 doi: 10.1002/14651858.CD005511.pub2[published Online First: Epub Date]|.

29. Schwendicke F, Stolpe M. Secondary Treatment for Asymptomatic Root Canal Treated Teeth: A Cost-effectiveness Analysis. Journal of endodontics 2015;**41**(6):812-6 doi: 10.1016/j.joen.2015.01.013[published Online First: Epub Date]|.
30. Paredes-Vieyra J, Enriquez FJ. Success rate of single- versus two-visit root canal treatment of teeth with apical periodontitis: a randomized controlled trial. Journal of endodontics 2012;**38**(9):1164-9 doi: 10.1016/j.joen.2012.05.021[published Online First: Epub Date]|.
31. Wong AW, Zhang C, Chu CH. A systematic review of nonsurgical single-visit versus multiple-visit endodontic treatment. Clinical, cosmetic and investigational dentistry 2014;**6**:45-56 doi: 10.2147/ccide.s61487[published Online First: Epub Date]|.
32. Ghoddusi J, Javidi M, Zarrabi MH, et al. Flare-ups incidence and severity after using calcium hydroxide as intracanal dressing. The New York state dental journal 2006;**72**(4):24-8
33. Albashaireh ZS, Alnegrish AS. Postobturation pain after single- and multiple-visit endodontic therapy. A prospective study. Journal of dentistry 1998;**26**(3):227-32
34. Jabeen S, Khurshiduzzaman M. Incidence of post obturation pain following single and multi visit root canal treatment in a teaching hospital of Bangladesh. Mymensingh medical journal : MMJ 2014;**23**(2):254-60
35. Sathorn C, Parashos P, Messer H. The prevalence of postoperative pain and flare-up in single- and multiple-visit endodontic treatment: a systematic review. International endodontic journal 2008;**41**(2):91-9 doi: 10.1111/j.1365-2591.2007.01316.x[published Online First: Epub Date]|.
36. Oginni A, Udoye CI. Endodontic flare-ups: comparison of incidence between single and multiple visits procedures in patients attending a Nigerian teaching hospital. Odonto-stomatologie tropicale = Tropical dental journal 2004;**27**(108):23-7

Figures

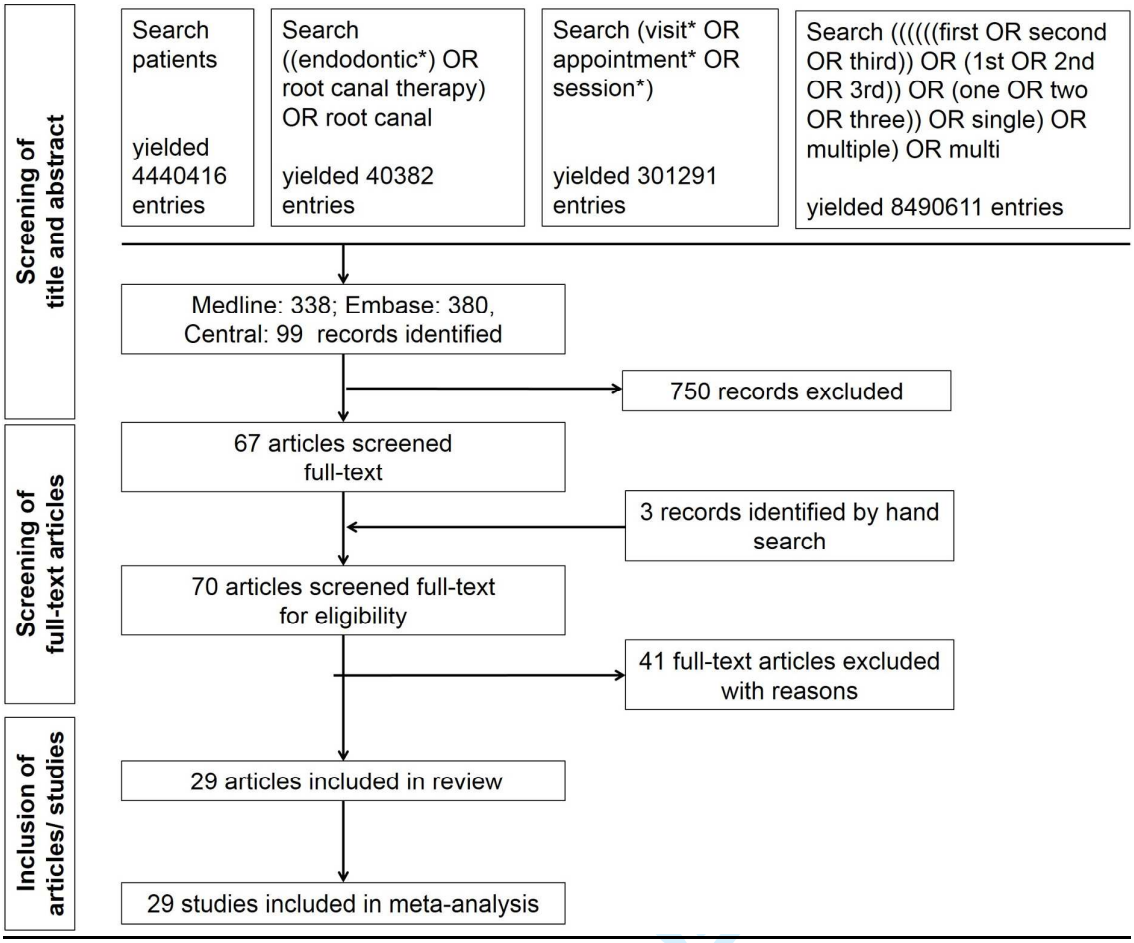

Figure 1: Study flow. Database screening was performed using a four-pronged search strategy, combining four domains of the search using Boolean operators. Number of studies yielded in Medline by each search domain are shown in the upper boxes; combining these boxes led to the number of results as shown for each database.

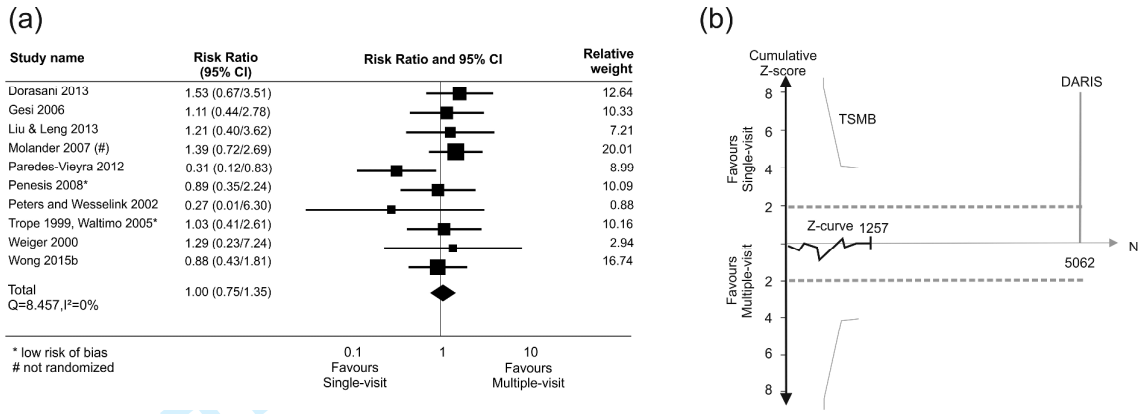

Figure 2: Risk of long-term complications after single- versus multiple-visit root-canal treatment. (a) Forest plot, with Risk Ratio (RR) and 95% confidence intervals (CI) per study and overall (black diamond) being given. Heterogeneity across studies is indicated by I^2 and Q. Low risk of bias and lack of random allocation of treatment is indicated by asterisks and hashtag. (b) Trial sequential analysis. The cumulative Z-score (black), i.e., the accumulated level of significance, was plotted against the number of participants (N) accrued, which was compared with the diversity-adjusted required information size (DARIS). The Z-curve does not cross the conventional thresholds for superiority or inferiority (hatched grey lines). Neither the DARIS nor TSMB (grey solid lines) were reached. The information fraction was too small to draw trial sequential futility boundaries.

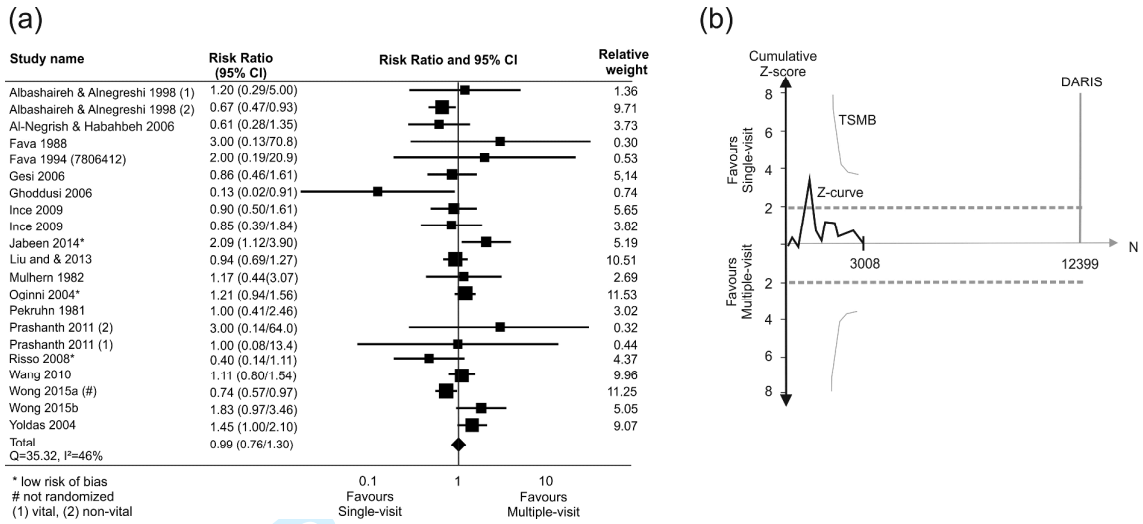

Figure 3: Risk of experiencing any postoperative pain after single- versus multiple-visit root-canal treatment. (a) Forest plot. Low risk of bias and lack of random allocation of treatment is indicated by asterisks and hashtag. Studies which compared treatments in different subgroup of teeth were handled as independent studies and are indicated accordingly. (b) Trial sequential analysis. The information fraction was too small to draw trial sequential futility boundaries.

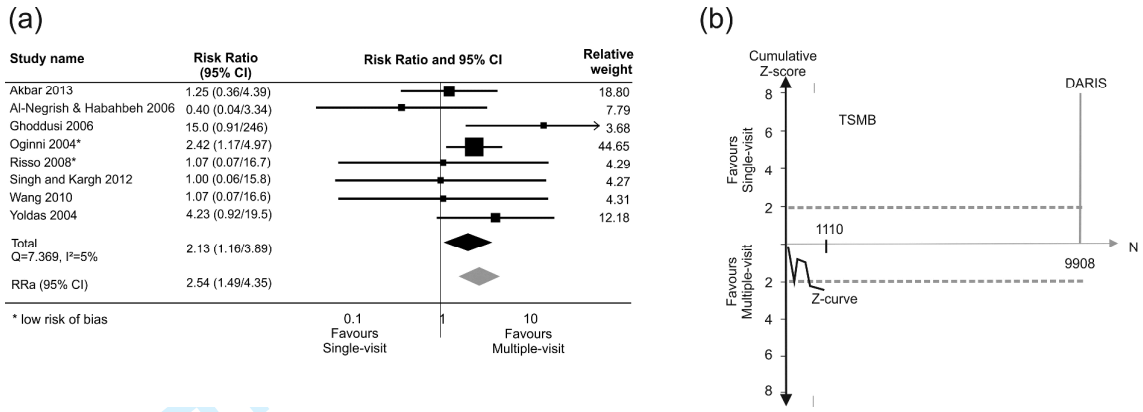

Figure 4: Risk of experiencing flare-up after single- versus multiple-visit root-canal treatment. (a) Forest plot. RR and 95% CI were adjusted for publication bias using trim-and-fill (RRa). Low risk of bias and lack of random allocation of treatment is indicated by asterisks and hashtag. Studies which compared treatments in different subgroup of teeth were handled as independent studies and are indicated accordingly. (b) Trial sequential analysis. The information fraction was too small to draw trial sequential futility boundaries.

Appendix

Syntheses methods

Unit-of analysis issues were handled as follows: In studies reporting on more than two treatment groups, three approaches were taken to avoid unit-of-analysis conflicts: In case of groups being comparable, we combined them. If additional groups used treatments not in accordance with current standard (e.g. multiple-step treatment without any root-canal medication), this group was omitted. If a factorial design was used (e.g. both groups were compared in vital and non-vital teeth), with separate reporting for all groups, we compared subgroups and handled them as if they were separate studies for meta-analysis.

Meta-regression was additionally performed. As some studies did not clearly state randomization (see above), a sensitivity analysis excluding these studies was performed. Similarly, as some studies reported results to have not been significantly different (but did not report on exact effect estimates), we imputed the number of events per group as the mean event rate in a sensitivity analysis, making best use of all available information. For subgroup comparisons, Chi-square test was performed. For meta-regression, the unrestricted maximum-likelihood method was used; Bonferroni adjustment to correct for multiple testing was planned, but not required, as no significant associations were found even without such correction.

Trial sequential analysis was performed. RIS was calculated based on type I error risk of $\alpha=0.05$ and a type II error risk of $\beta=0.20$ (equivalent to a power of 0.80). The control event proportion (i.e. event incidence in multiple-visit group) and the relative risk reduction (RRR) were used to estimate RIS. RRR was based on an a priori defined worthwhile interventional effect of 20% (lower effects might be worthwhile, but would increase RIS even further) (1, 2). RIS was diversity (heterogeneity) adjusted (DARIS). To assess if differences yielded by conventional meta-analysis are robust, TSA additionally estimates trial sequential monitoring boundaries (TSMB), i.e. statistical thresholds for significance which are adapted depending on the so far reached sample size. The Lan-DeMets version (3) of the O'Brien–Fleming

function (4) was used for calculating the TSMBs. In case the cumulative Z-value crossed the conventional boundary of significance (Z=±1.96) but not the TSMBs for benefit or harm, we defined such findings as spuriously significant. Firm evidence was assumed to be reached when the Z-curve crossed the TSMB for benefit or harm before the DARIS was reached. Effect estimates supported by only few small trials are thus handled stricter than those supported by large samples. In addition to such superiority/inferiority TSMBs, monitoring boundaries for futility were calculated (these indicate if further trial conduct is likely to be futile, i.e. if sufficient evidence has been accrued to claim non-inferiority of treatments). Further details regarding the applied method to calculate TSMB have been reported elsewhere (1). TSA was performed with TSA 0.9 (Copenhagen Trial Unit, Copenhagen, Denmark) (5).

Table S1: Excluded Studies

Soltanoff 1978 (6)	No RCT
O'Keefe 1976 (7)	No RCT
ElMubarak 2010 (8)	No RCT
Raju 2014 (9)	Did not compare 1- vs 2 visits
Xavier 2013 (10)	No clinical outcome
Bhagwat 2013 (11)	Did not compare 1- vs 2 visits
Roane 1983 (12)	No RCT
Oliet 1983 (13)	No RCT
Ether 1978 (14)	Not available
Eleazer 1998 (15)	no RCT
Fava 1989 (16)	Compared different techniques
Fox 1970 (17)	no RCT
Genet 1986 (18)	no RCT
Morse 1987 (19)	Did not compare 1- vs 2 visits
Yesilsoy 1988 (20)	Did not compare 1- vs 2 visits
Trope 1991 (21)	Did not compare 1- vs 2 visits
Koba 1999 (22)	Did not compare 1- vs 2 visits
Glennon 2004 (23)	no RCT
Ng 2004 (24)	no RCT
Georgopoulou 1986 (25)	no RCT
Jurcak 1993 (26)	no RCT
Imura 1995 (27)	no RCT
Walton 1992 (28)	no RCT
Alacam 1985 (29)	Did not compare 1- vs 2 visits
Torabinejad 1994 (30)	Did not compare 1- vs 2 visits
Sjögren 1990 (31)	Did not compare 1- vs 2 visits
Siqueira 2002 (32)	Did not compare 1- vs 2 visits
Orstavik 1996 (33)	Did not compare 1- vs 2 visits
Perkruhn 1986 (34)	Did not compare 1- vs 2 visits
Kvist 2004 (35)	no clinical outcomes reported (CFU)
Rudner 1981 (36)	no RCT
Kenrick 1999 (37)	no RCT
Sjögren 1997 (38)	Did not compare 1- vs 2 visits
Maddox 1977 (39)	Did not compare 1- vs 2 visits
Sjögren 1990 (31)	no RCT
Glennon 2004 (23)	no RCT
Fleming 2010 (40)	no RCT
Singla 2008 (41)	pulpectomy
Kalhoro 2009 (42)	no RCT
Shaikh 2013 (43)	Not available

Table S2: Risk of bias of included studies. Bias assessment followed guidelines outline by The Cochrane Collaboration (44).

	Sequence generation	Allocation Concealment	Blinding of operator	Blinding of examiner	Incomplete data	Selective reporting	Overall risk of bias
Akbar 2013 (45)	Unclear	Unclear	High	Low	Low	Low	Unclear/High
Albashaireh & Alnegreshi 1998 (46)	Unclear	Unclear	High	Low	Low	Low	Unclear/High
Al-Negrish & Habahbeh 2006 (47)	Unclear	Unclear	High	High	Low	Low	Unclear/High
DiRenzo 2002 (48)	Low	Low	Low	Low	Low	Low	Low
Dorsani 2013 (49)	Unclear	Unclear	High	Low	Low	Low	Unclear/High
Fava 1989 (50)	Unclear	Unclear	High	Low	Low	Low	Unclear/High
Fava 1994 (51)	Unclear	Unclear	High	Low	Low	Low	Unclear/High
Gesi 2006 (52)	Low	Low	High	Low	Low	Low	Unclear/High
Ghoddusi 2006 (53)	Unclear	Unclear	High	Low	Low	Low	Unclear/High
Ince 2009 (54)	Unclear	Unclear	Unclear	Low	Low	Low	Unclear/High
Jabeen 2014 (55)	Low	Low	Low	Low	Low	Low	Low
Liu & Leng 2013 (56)	Unclear	Unclear	High	Low	Low	Low	Unclear/High
Molander 2007 (57)	High	Unclear	High	Low	Low	Low	Unclear/High
Mulhern 1982 (58)	Low	Low	High	Low	Low	Low	Unclear/High
Oginni 2004 (59)	Low	Low	Low	Low	Low	Low	Low
Paredes-Vieyra 2012 (60)	Unclear	High	High	Low	Low	Low	Unclear/High
Pekruhn 1981 (61)	Unclear	Unclear	Unclear	Low	Low	Low	Unclear/High
Penesis 2008 (62)	Low	Low	Low	Low	Low	Low	Low
Peters and Wesslink 2002 (63)	Low	Unclear	High	Low	Low	Low	Unclear/High
Prashanth 2011 (64)	Unclear	High	High	High	High	Low	Unclear/High
Rao 2014 (65)	Unclear	High	Low	Low	Low	Low	Unclear/High
Risso 2008 (66)	Low	Low	Low	Low	Low	Low	Low
Singh and Kargh 2012 (67)	Unclear	High	Low	Low	Low	Low	Unclear/High
Trope 1999 (68), Waltimo 2005 (69)	Low	Low	Low	Low	Low	Low	Low
Wang 2010 (70)	Low	Low	High	High	Low	Low	Unclear/High
Weiger 2000 (71)	Unclear	High	High	Low	Low	Low	Unclear/High
Wong 2015a (72)	High	High	Low	Low	Low	High	Unclear/High
Wong 2015b (73)	Low	Unclear	High	High	Low	Low	Unclear/High
Yoldas 2004 (74)	Unclear	Unclear	High	Low	Low	Low	Unclear/High

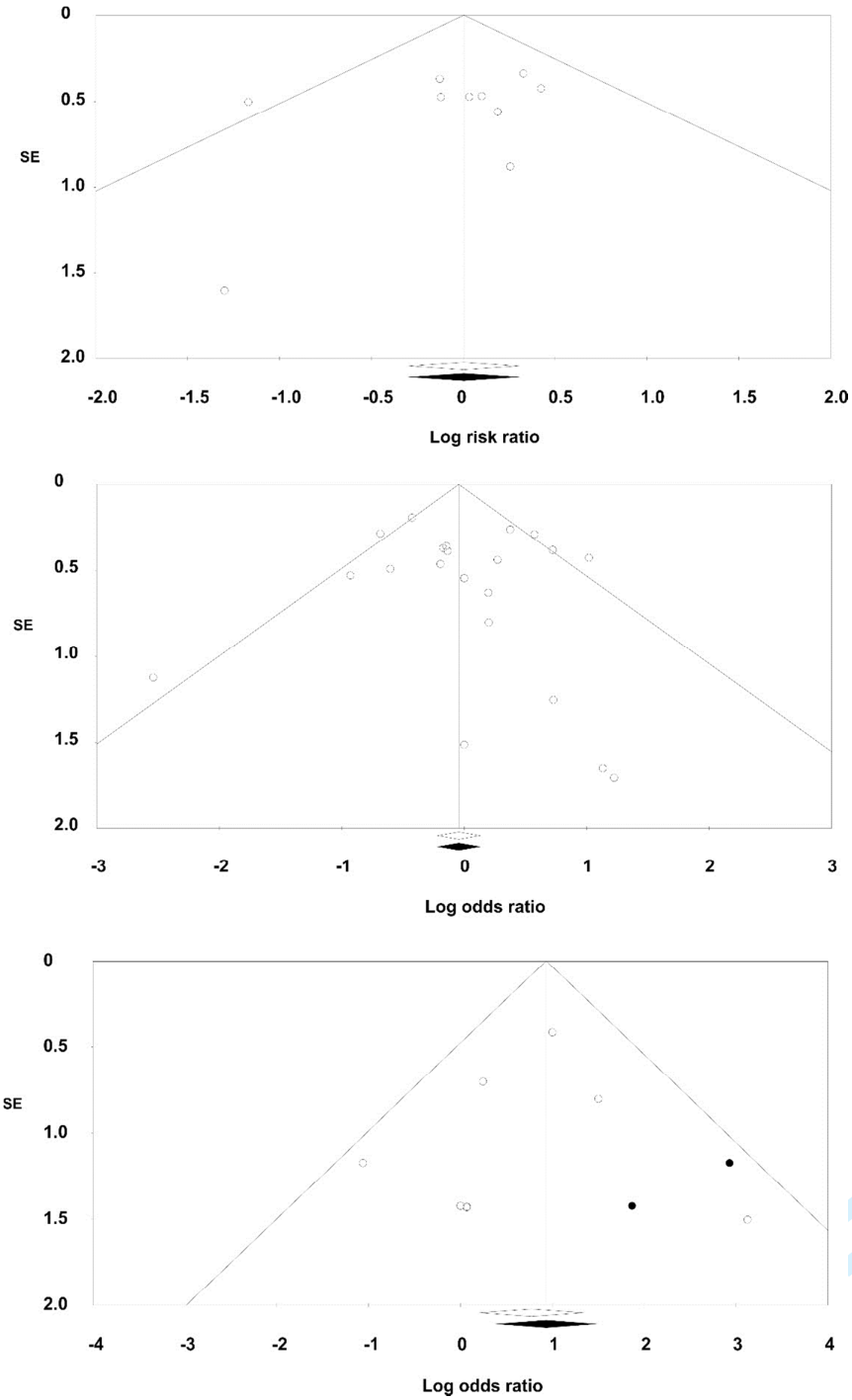

Figure S1: Funnel plots. (a) Risk long-term complications, (b) risk of experiencing any postoperative pain, (c) risk of experiencing a flare-up. Standard errors are plotted against logRR to estimate possible small study effects or publication bias via an asymmetry of the funnel. White circles: estimates reported by included studies, black balls: imputed estimates in case of suspected publication bias. White diamond: effect estimate based on included studies, black diamond: effect estimate based on included and imputed studies.

References for the appendix

1. Schwendicke F, Goestemeyer G, Gluud C. Cavity lining after excavating caries lesions: meta-analysis and trial sequential analysis of randomized clinical trials. *Journal of Dentistry* 2015;**doi: 10.1016/j.jdent.2015.07.017**.
2. Schwendicke F, Karimbux N, Allareddy V, Gluud C. Periodontal treatment for preventing adverse pregnancy outcomes: a meta- and trial sequential analysis. *PloS one* 2015;**10**(6):e0129060.
3. Demets DL, Lan KKG. Interim analysis: The alpha spending function approach. *Statistics in medicine* 1994;**13**(13-14):1341-52.
4. O'Brien PC, Fleming TR. A Multiple Testing Procedure for Clinical Trials. *Biometrics* 1979;**35**(3):549-56.
5. Thorlund K, Engstrøm J, Wetterslev J, Brok J, Imberger G, Gluud C. User Manual for Trial Sequential Analysis (TSA). http://www.ctu.dk/tsa/files/tsa_manual.pdf 2011:1-115.
6. Soltanoff W. A comparative study of the single-visit and the multiple-visit edodontic procedure. *Journal of endodontics* 1978;**4**(9):278-81.
7. O'Keefe EM. Pain in endodontic therapy: preliminary study. *Journal of endodontics* 1976;**2**(10):315-9.
8. El Mubarak AH, Abu-bakr NH, Ibrahim YE. Postoperative pain in multiple-visit and single-visit root canal treatment. *Journal of endodontics* 2010;**36**(1):36-9.
9. Raju TB, Seshadri A, Vamsipavani B, Abhilash K, Subhash AV, Kumari KV. Evaluation of pain in single and multi rooted teeth treated in single visit endodontic therapy. *Journal of international oral health : JIOH* 2014;**6**(1):27-32.
10. Xavier AC, Martinho FC, Chung A, Oliveira LD, Jorge AO, Valera MC, et al. One-visit versus two-visit root canal treatment: effectiveness in the removal of endotoxins and cultivable bacteria. *Journal of endodontics* 2013;**39**(8):959-64.
11. Bhagwat S, Mehta D. Incidence of post-operative pain following single visit endodontics in vital and non-vital teeth: An in vivo study. *Contemporary clinical dentistry* 2013;**4**(3):295-302.
12. Roane JB, Dryden JA, Grimes EW. Incidence of postoperative pain after single- and multiple-visit endodontic procedures. *Oral surgery, oral medicine, and oral pathology* 1983;**55**(1):68-72.
13. Oliet S. Single-visit endodontics: a clinical study. *Journal of endodontics* 1983;**9**(4):147-52.
14. al. ESe. A comparison of one and two visit endodontics. *J Farmacia Odontol* 1978(8):215.
15. Eleazer PD, Eleazer KR. Flare-up rate in pulpally necrotic molars in one-visit versus two-visit endodontic treatment. *Journal of endodontics* 1998;**24**(9):614-6.
16. Fava LR. One-appointment root canal treatment: incidence of postoperative pain using a modified double-flared technique. *International endodontic journal* 1991;**24**(5):258-62.
17. Fox J, Atkinson JS, Dinin AP, Greenfield E, Hechtman E, Reeman CA, et al. Incidence of pain following one-visit endodontic treatment. *Oral surgery, oral medicine, and oral pathology* 1970;**30**(1):123-30.
18. Genet JM, Wesselink PR, Thoden van Velzen SK. The incidence of preoperative and postoperative pain in endodontic therapy. *International endodontic journal* 1986;**19**(5):221-9.
19. Morse DR, Furst ML, Belott RM, Lefkowitz RD, Spritzer IB, Sideman BH. Infectious flare-ups and serious sequelae following endodontic treatment: a prospective randomized

trial on efficacy of antibiotic prophylaxis in cases of asymptomatic pulpal-periapical lesions. *Oral surgery, oral medicine, and oral pathology* 1987;**64**(1):96-109.
20. Yesilsoy C, Koren LZ, Morse DR, Rankow H, Bolanos OR, Furst ML. Post-endodontic obturation pain: a comparative evaluation. *Quintessence international* 1988;**19**(6):431-8.
21. Trope M. Flare-up rate of single-visit endodontics. *International endodontic journal* 1991;**24**(1):24-6.
22. Koba K, Kimura Y, Matsumoto K, Watanabe H, Shinoki T, Kojy R, et al. Post-operative symptoms and healing after endodontic treatment of infected teeth using pulsed Nd:YAG laser. *Endodontics & dental traumatology* 1999;**15**(2):68-72.
23. Glennon JP, Ng YL, Setchell DJ, Gulabivala K. Prevalence of and factors affecting postpreparation pain in patients undergoing two-visit root canal treatment. *International endodontic journal* 2004;**37**(1):29-37.
24. Ng YL, Glennon JP, Setchell DJ, Gulabivala K. Prevalence of and factors affecting post-obturation pain in patients undergoing root canal treatment. *International endodontic journal* 2004;**37**(6):381-91.
25. Georgopoulou M, Anastassiadis P, Sykaras S. Pain after chemomechanical preparation. *International endodontic journal* 1986;**19**(6):309-14.
26. Jurcak JJ, Bellizzi R, Loushine RJ. Successful single-visit endodontics during Operation Desert Shield. *Journal of endodontics* 1993;**19**(8):412-3.
27. Imura N, Zuolo ML. Factors associated with endodontic flare-ups: a prospective study. *International endodontic journal* 1995;**28**(5):261-5.
28. Walton R, Fouad A. Endodontic interappointment flare-ups: a prospective study of incidence and related factors. *Journal of endodontics* 1992;**18**(4):172-7.
29. Alacam T. Incidence of postoperative pain following the use of different sealers in immediate root canal filling. *Journal of endodontics* 1985;**11**(3):135-7.
30. Torabinejad M, Cymerman JJ, Frankson M, Lemon RR, Maggio JD, Schilder H. Effectiveness of various medications on postoperative pain following complete instrumentation. *Journal of endodontics* 1994;**20**(7):345-54.
31. Sjogren U, Hagglund B, Sundqvist G, Wing K. Factors affecting the long-term results of endodontic treatment. *Journal of endodontics* 1990;**16**(10):498-504.
32. Siqueira JF, Jr., Rocas IN, Favieri A, Machado AG, Gahyva SM, Oliveira JC, et al. Incidence of postoperative pain after intracanal procedures based on an antimicrobial strategy. *Journal of endodontics* 2002;**28**(6):457-60.
33. Orstavik D. Time-course and risk analyses of the development and healing of chronic apical periodontitis in man. *International endodontic journal* 1996;**29**(3):150-5.
34. Pekruhn RB. The incidence of failure following single-visit endodontic therapy. *Journal of endodontics* 1986;**12**(2):68-72.
35. Kvist T, Molander A, Dahlen G, Reit C. Microbiological evaluation of one- and two-visit endodontic treatment of teeth with apical periodontitis: a randomized, clinical trial. *Journal of endodontics* 2004;**30**(8):572-6.
36. Rudner WL, Oliet S. Single-visit endodontics: a concept and a clinical study. *Compendium of continuing education in dentistry (Jamesburg, N.J. : 1995)* 1981;**2**(2):63-8.
37. Kenrick S. Endodontics: a multiple-visit or single-visit approach. *Australian endodontic journal : the journal of the Australian Society of Endodontology Inc* 2000;**26**(2):82-5.
38. Sjogren U, Figdor D, Persson S, Sundqvist G. Influence of infection at the time of root filling on the outcome of endodontic treatment of teeth with apical periodontitis. *International endodontic journal* 1997;**30**(5):297-306.

39. Maddox D, Walton R, Davis C. Incidence of posttreatment endodontic pain related to medication and other factors. *Journal of endodontics* 1977;**3**(12):447-52.
40. Fleming CH, Litaker MS, Alley LW, Eleazer PD. Comparison of classic endodontic techniques versus contemporary techniques on endodontic treatment success. *Journal of endodontics* 2010;**36**(3):414-8.
41. Singla R, Marwah N, Dutta S. Single Visit versus Multiple Visit Root Canal Therapy. *International journal of clinical pediatric dentistry* 2008;**1**(1):17-24.
42. Kalhoro FA, Mirza AJ. A study of flare-ups following single-visit root canal treatment in endodontic patients. *Journal of the College of Physicians and Surgeons--Pakistan : JCPSP* 2009;**19**(7):410-2.
43. Shaikh AG, Kalhoro FA, Dall AQ. Evaluation of post operative pain in single and multi visit endodontic therapy with rotary instruments. *Medical Forum Monthly* 2013;**24**(1):49-54.
44. Higgins JPT, Green S, editors. Cochrane Handbook for Systematic Reviews of Interventions. Version 5.10 (updated March 2011): The Cochrane Collaboration; 2011.
45. Akbar I, Iqbal A, Al-Omiri MK. Flare-up rate in molars with periapical radiolucency in one-visit vs two-visit endodontic treatment. *The journal of contemporary dental practice* 2013;**14**(3):414-8.
46. Albashaireh ZS, Alnegrish AS. Postobturation pain after single- and multiple-visit endodontic therapy. A prospective study. *Journal of dentistry* 1998;**26**(3):227-32.
47. Al-Negrish AR, Habahbeh R. Flare up rate related to root canal treatment of asymptomatic pulpally necrotic central incisor teeth in patients attending a military hospital. *Journal of dentistry* 2006;**34**(9):635-40.
48. DiRenzo A, Gresla T, Johnson BR, Rogers M, Tucker D, BeGole EA. Postoperative pain after 1- and 2-visit root canal therapy. *Oral surgery, oral medicine, oral pathology, oral radiology, and endodontics* 2002;**93**(5):605-10.
49. Dorasani G, Madhusudhana K, Chinni SK. Clinical and radiographic evaluation of single-visit and multi-visit endodontic treatment of teeth with periapical pathology: An in vivo study. *Journal of conservative dentistry : JCD* 2013;**16**(6):484-8.
50. Fava LR. A comparison of one versus two appointment endodontic therapy in teeth with non-vital pulps. *International endodontic journal* 1989;**22**(4):179-83.
51. Fava LR. A clinical evaluation of one and two-appointment root canal therapy using calcium hydroxide. *International endodontic journal* 1994;**27**(1):47-51.
52. Gesi A, Hakeberg M, Warfvinge J, Bergenholtz G. Incidence of periapical lesions and clinical symptoms after pulpectomy--a clinical and radiographic evaluation of 1- versus 2-session treatment. *Oral surgery, oral medicine, oral pathology, oral radiology, and endodontics* 2006;**101**(3):379-88.
53. Ghoddusi J, Javidi M, Zarrabi MH, Bagheri H. Flare-ups incidence and severity after using calcium hydroxide as intracanal dressing. *The New York state dental journal* 2006;**72**(4):24-8.
54. Ince B, Ercan E, Dalli M, Dulgergil CT, Zorba YO, Colak H. Incidence of postoperative pain after single- and multi-visit endodontic treatment in teeth with vital and non-vital pulp. *European journal of dentistry* 2009;**3**(4):273-9.
55. Jabeen S, Khurshiduzzaman M. Incidence of post obturation pain following single and multi visit root canal treatment in a teaching hospital of Bangladesh. *Mymensingh medical journal : MMJ* 2014;**23**(2):254-60.
56. Liu S, Leng Z-y. Short-term clinical effect of single-visit root-canal therapy in infected root canals. *Journal of Shanghai Jisobong University* 2013;**33**(7):1014-17.

57. Molander A, Warfvinge J, Reit C, Kvist T. Clinical and radiographic evaluation of one- and two-visit endodontic treatment of asymptomatic necrotic teeth with apical periodontitis: a randomized clinical trial. *Journal of endodontics* 2007;**33**(10):1145-8.
58. Mulhern JM, Patterson SS, Newton CW, Ringel AM. Incidence of postoperative pain after one-appointment endodontic treatment of asymptomatic pulpal necross in single-rooted teeth. *Journal of endodontics* 1982;**8**(8):370-5.
59. Oginni A, Udoye CI. Endodontic flare-ups: comparison of incidence between single and multiple visits procedures in patients attending a Nigerian teaching hospital. *Odonto-stomatologie tropicale = Tropical dental journal* 2004;**27**(108):23-7.
60. Paredes-Vieyra J, Enriquez FJ. Success rate of single- versus two-visit root canal treatment of teeth with apical periodontitis: a randomized controlled trial. *Journal of endodontics* 2012;**38**(9):1164-9.
61. Pekruhn RB. Single-visit endodontic therapy: a preliminary clinical study. *Journal of the American Dental Association (1939)* 1981;**103**(6):875-7.
62. Penesis VA, Fitzgerald PI, Fayad MI, Wenckus CS, BeGole EA, Johnson BR. Outcome of one-visit and two-visit endodontic treatment of necrotic teeth with apical periodontitis: a randomized controlled trial with one-year evaluation. *Journal of endodontics* 2008;**34**(3):251-7.
63. Peters LB, Wesselink PR. Periapical healing of endodontically treated teeth in one and two visits obturated in the presence or absence of detectable microorganisms. *International endodontic journal* 2002;**35**(8):660-7.
64. Prashanth MB, Tavane PN, Abraham S, Chacko L. Comparative evaluation of pain, tenderness and swelling followed by radiographic evaluation of periapical changes at various intervals of time following single and multiple visit endodontic therapy: an in vivo study. *The journal of contemporary dental practice* 2011;**12**(3):187-91.
65. Rao KN, Kandaswamy R, Umashetty G, Rathore VP, Hotkar C, Patil BS. Post-Obturation pain following one-visit and two-visit root canal treatment in necrotic anterior teeth. *Journal of international oral health : JIOH* 2014;**6**(2):28-32.
66. Risso PA, Cunha AJ, Araujo MC, Luiz RR. Postobturation pain and associated factors in adolescent patients undergoing one- and two-visit root canal treatment. *Journal of dentistry* 2008;**36**(11):928-34.
67. Singh S, Garg A. Incidence of post-operative pain after single visit and multiple visit root canal treatment: A randomized controlled trial. *Journal of conservative dentistry : JCD* 2012;**15**(4):323-7.
68. Trope M, Delano EO, Orstavik D. Endodontic treatment of teeth with apical periodontitis: single vs. multivisit treatment. *Journal of endodontics* 1999;**25**(5):345-50.
69. Waltimo T, Trope M, Haapasalo M, Orstavik D. Clinical efficacy of treatment procedures in endodontic infection control and one year follow-up of periapical healing. *Journal of endodontics* 2005;**31**(12):863-6.
70. Wang C, Xu P, Ren L, Dong G, Ye L. Comparison of post-obturation pain experience following one-visit and two-visit root canal treatment on teeth with vital pulps: a randomized controlled trial. *International endodontic journal* 2010;**43**(8):692-7.
71. Weiger R, Rosendahl R, Lost C. Influence of calcium hydroxide intracanal dressings on the prognosis of teeth with endodontically induced periapical lesions. *International endodontic journal* 2000;**33**(3):219-26.
72. Wong AW, Zhang S, Li SK, Zhu X, Zhang C, Chu CH. Incidence of post-obturation pain after single-visit versus multiple-visit non-surgical endodontic treatments. *BMC oral health* 2015;**15**:96.

73. Wong AW, Tsang CS, Zhang S, Li KY, Zhang C, Chu CH. Treatment outcomes of single-visit versus multiple-visit non-surgical endodontic therapy: a randomised clinical trial. *BMC oral health* 2015;**15**(1):162.

74. Yoldas O, Topuz A, Isci AS, Oztunc H. Postoperative pain after endodontic retreatment: single- versus two-visit treatment. *Oral surgery, oral medicine, oral pathology, oral radiology, and endodontics* 2004;**98**(4):483-7.

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	3
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	3
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	5-6
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	6
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	6
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	6-7
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	7
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Fig 1
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	Fig 1
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	8
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	8
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	9
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	9-10
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	9-10

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	9-10
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	9-10
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	Fig 1
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	Tab. 1
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	Tab. S2
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	Fig. 2-4
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	Fig. 2-4
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	Tab S2
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	Fig 2-4
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	13-15
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	15-16
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	16-17
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	17

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

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Single- or multiple visit root-canal treatment: Systematic Review, Meta-Analysis and Trial Sequential Analysis

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Single- or multiple visit root-canal treatment: Systematic Review, Meta-Analysis and Trial Sequential Analysis

Abstract

Objectives: Single-visit root-canal treatment has some advantages over conventional multi-visit treatment, but might increase the risk of complications. We systematically evaluated the risk of complications after single- or multiple visit root-canal treatment using meta- and trial-sequential analysis

Data: Controlled trials comparing single- versus multiple-visit root-canal treatment of permanent teeth were included. Trials needed to assess the risk of long-term complications (pain, infection, new/persisting/increasing peri-apical lesions ≥1 year after treatment), short-term pain, or flare-up (acute exacerbation of commencement or continuation of root-canal treatment).

Sources: Electronic databases (PubMed, Embase, Cochrane Central) were screened, random-effects meta-analyses performed, and trial-sequential analysis used to control for risk of random errors. Evidence was graded according to GRADE.

Study selection: 29 trials (4341 patients) were included, all but six showing high risk of bias. Based on ten trials (1257 teeth), risk of complications was not significantly different in single- versus multiple-visit treatment (RR: 1.00 [95% CI: 0.75/1.35]; weak evidence). Based on twenty studies (3008 teeth), risk of pain did not significantly differ between treatments (RR: 0.99 [95% CI: 0.76/1.30]; moderate evidence). Risk of flare-up was recorded by eight studies (1110 teeth) and was significantly higher after single- versus multiple-visit treatment (RR: 2.13 [95% CI: 1.16/3.89]; very weak evidence). Trial-sequential analysis revealed that firm evidence for benefit, harm or futility was not reached for any of the outcomes.

Conclusions: There is insufficient evidence to rule out whether important differences between both strategies exist.

Clinical significance: Dentists can provide root-canal treatment in one or multiple visits. Given the possibly increased risk of flare-ups, multiple-visit treatment might be preferred for certain teeth (e.g. those with peri-apical lesions).

Strength and limitations of this study

- This registered systematic review applies meta- and trial-sequential analysis to assess the strength and quantity of the accrued evidence towards different root-canal treatment strategies.
- The synthesized estimates are supported only by moderate or weak evidence according to GRADE.
- Firm evidence for benefit or harm of single- or multiple visit root-canal therapy as well as futility of further trials was not reached.

Introduction

After root-canal treatment, teeth can experience short- and/or long-term complications. Short-term complications include postoperative inflammation of peri-apical tissues leading to mild pain, or flare-up (i.e. an acute exacerbation of pulpal or peri-apical pathosis after root-canal treatment, like severe unbearable pain and swelling). Pain and swelling have been associated with instrumentation or irrigation transporting medications, infected debris and bacteria into the peri-apical tissues. Inadequate instrumentation and disinfection lead to bacterial persistence within the root-canals and consequent (re)contamination of peri-apical tissue.[1 2] Long-term outcomes include persisting inflammation and infection, resulting in abscess, sinus track formation, radiographic signs of peri-apical bone resorption or severe pain, with subsequent need to endodontically re-treat or remove teeth.[3 4] Both short and long-term outcomes seem to be affected by the preoperative condition of the tooth (tooth type, vitality, symptoms, peri-apical conditions).[4] Moreover, they might be affected by how root-canal treatments are provided.

Single-visit root-canal treatment attempts instrumentation, disinfection and obturation of the root-canal system in one visit. In contrast, multiple-visit root-canal treatment performs the instrumentation (or large parts of it) in the first and the obturation in the second visit, while the disinfection is provided in both visits via irrigation. Moreover, a disinfecting medication is placed in the canals between visits to allow further reduction of bacterial numbers. While single-visit treatment has obvious advantages over conventional multiple-visit treatment (like reduced number of visits, no need for repeated application of anesthetics or rubberdam, no intermediary restoration), it might be disadvantageous both with regards to short and long term outcomes.

A number of reviews have compared single- versus multiple visit root-canal treatment.[3 5-8] Some of these are outdated,[3 6] others investigate only short-term pain as outcome,[5] again others build on evidence beyond controlled trials like cohort studies or expert

opinions,[7] or pooled short- and long-term outcomes, which does not allow to weigh them against each other.[8] The present review aimed to comprehensively compare the currently available controlled trial data on short- and long-term complications of single- versus multiple visit root-canal treatment. Our primary objective was to answer the question: In patients needing root-canal treatment, is single-visit treatment significantly more effective than multiple visit treatment with regards to risk of long-term failure? The secondary objective was to compare both treatments with regards to risk of short-term postoperative pain as well as the risk of flare-up. We further investigated moderators of risks using subgroup or meta-regression analysis, and assessed how statistically robust current evidence is with regards to type I or II errors using trial sequential analysis. The review should guide the conduct of further studies and help to deduct clinical recommendations.

Methods

Eligibility criteria

This systematic review (registered at PROSPERO CRD42016036386) included trials that

- were randomized controlled trials or controlled trials without signs of selection bias (i.e. treatments were not allocated according to preoperative tooth status etc.). Sensitivity analyses were performed to account for the introduced risk of bias in case of treatment allocation not being at random.
- compared single-visit with multiple visit root-canal treatment in permanent teeth with closed apices and without internal resorption, regardless of the pre-operative condition (meta-regression and subgroup analyses were performed to account for different conditions).
- reported on risk of long-term complications (≥1 year after treatment), and/or risk of experiencing any short-term pain, and/or risk of short-term flare-up.

Outcomes

The primary outcome was the risk of long-term complications, defined as pain, infection/swelling/sinus track formation, or development, persistence or aggravation of peri-apical lesions or widening of the periodontal ligament etc. ≥1 year after treatment. No standard as to how peri-apical lesions needed to be assessed or categorized was set, as a range of classification systems are currently used.[3] Note that against our protocol, we did not assess the need of re-treatment due to long-term complications, as in most included trials it was not clearly stated, if re-treatments have been performed.

The secondary outcomes were

- risks of experiencing any short-term pain (<1 year after treatment) after obturation or after instrumentation or after both. For comparison of treatments, we considered only pain after obturation, not after instrumentation without obturation during multiple visit treatment. To detect the largest difference between treatments, incidence of pain was extracted at the shortest recording time point after treatment. As we did not separate mild, moderate or severe pain, and even included outcome measures like having taken any pain medication in this outcome, risk of any pain does not necessarily indicate a further treatment being required. Moreover, it should be noted that different degrees of pain where pooled. This was not avoidable given the different scales used, which cannot be synthesized otherwise., but introduces additional heterogeneity.
- risks of experiencing short-term flare-up, usually defined as an acute exacerbation of an asymptomatic pulpal and/or periradicular pathosis after the initiation or continuation of root canal treatment [9]. .Note that flare-up was not defined consistently across studies; some studies reported flare-up whilst having treated both symptomatic and asymptomatic teeth. We therefore defined flare-up as a short-term symptom (<1 year, usually directly after commencement or conclusion of root-canal treatment) which led or can be assumed to lead to a further intervention (like re-

accessing/re-instrumenting an incomplete treatment; completing an incision and drainage procedure, or re-performing root-canal treatment).

Searches

We searched Medline via PubMed, Embase via Ovid and Cochrane Central on March 10th 2016. Moreover, opengrey.eu was searched to identify accepted, but not published studies. There was no date restriction in our search. In addition, reference lists of identified full-texts were screened and cross-referenced. We contacted study authors if required to obtain full-texts. Neither authors nor journals were blinded to reviewers. No language restriction was set.

The applied search strategy can be found in Fig. 1.

Study records

Data management

A piloted spreadsheet was used for data extraction and management.

Selection process

Two reviewers (FS, GG) independently screened titles and then compared their findings. In case of disagreement, titles were included to obtain full texts. Full texts were assessed independently after de-duplication. Studies were included after agreement with consensus in cases of disagreement being reached through discussion.

Data collection process

Data extraction was performed independently by two reviewers (FS, GG). Disagreements were resolved through discussion.

Data items

The following items were collected: Author names, year, sample, setting, tooth type, pulp vitality, preoperative pain, presence of radiographically detectable periapical lesions,

instrumentation type, obturation type, irrigation, medication, intermediate restoration, no of visits, evaluation method, findings.

Outcomes

Outcomes and outcome measures were extracted. For studies reporting non-significant findings without any further information, this was extracted to allow including these into a sensitivity meta-analysis (see below).

Data synthesis

Meta-analysis

The statistical unit was the tooth. Clustering was near absent in most studies. Therefore, the risk of this approach leading to artificially narrow confidence intervals is low.[10] A continuity correction of +1 was performed in case of zero events. Random-effects meta-analysis using the DerSimonian-Laird estimator of variance was performed using Comprehensive Meta-Analysis 2.2.64 (Biostat, Englewood, NJ, USA), with Risk Ratios (RR) and 95% confidence intervals (95% CI) as effect estimates. Fixed effect models were used as well, but did not yield significantly different findings given the low level of heterogeneity. Unit-of analysis issues were handled as described in the appendix. Heterogeneity was assessed using Cochran's Q and I^2-statistics.[11] Funnel plot analysis and Egger test were performed to assess small study effects or publication bias.[12 13] RR were adjusted (RRa) to check the impact of possible publication bias.[14]

Subgroup and meta-regression analyses

Subgroup and meta-regression analyses were carried out to assess (1) the impact of a root-canal medication being used (or not) in multiple-visit treatment, (2) pulp vitality prior treatment, (3) preoperative pain, and (4) the presence of radiographically detectable peri-apical lesions on effect estimates. Details can be found in the appendix.

Confidence in data

Risk of bias was assessed and classified according to Cochrane guidelines.[13] Note that against our protocol, we did not assess performance bias (blinding of operators), as this is not feasible in trials comparing single- versus multiple-visit treatment.

In addition, trial sequential analysis (TSA) was performed to assess if quantitative findings are robust, and to calculate the required information size (RIS), i.e. the cumulative sample size needed to yield significant differences between treatments.[15 16] RIS is then adjusted for heterogeneity/diversity (DARIS). TSA additionally estimates trial sequential monitoring boundaries (TSMB), i.e. statistical thresholds for significance which are adapted depending on the so far reached sample size. Firm evidence is assumed to be reached when the Z-curve crosses the TSMB for benefit or harm before the DARIS was reached. Effect estimates supported by only few small trials are handled stricter than those supported by large samples. In addition to such superiority/inferiority TSMBs, monitoring boundaries for futility were calculated. These indicate if further trial conduct is likely to be futile, i.e. if sufficient evidence has been accrued to claim non-inferiority of treatments (which would be most relevant for this review). Further details have been reported elsewhere,[17] and can also be found in the appendix.

Evidence for each outcome effect estimate was graded according to the GRADE working group of evidence,[18] using Grade Profiler 3.6, and strength of recommendations deduced accordingly.[19]

Results

Results of the searches

From 817 records, 64 were screened full-text. After cross-referencing 67 articles were screened and 29 included (Tab. 1).[8 20-48] Excluded studies and reasons for exclusion can be found in the appendix (Tab. S1).

Overall, 4341 (mainly adult) patients had been treated (Tab. 1).

Table 1: Included studies.

Study	Patients	Vital/ pain/ lesion	Instr.	Medication	Obtur.	No. of visits	Pain Pain/sample single-visit; Pain/sample multiple-visit; recall	Flare-up Flare-ups/sample single-visit; Flare-ups/sample multiple-visit; recall	Long-term complications Complications/sample single-visit; Complications/sample multiple-visit; recall
Akbar 2013 [20]	100 adults or adolescents	no/ unclear/ yes	hand	calcium hydroxide	lateral	2		5/50; 4/50; 7 days	
Albashaireh & Alnegreshi 1998 [21]	300 adults or adolescents	yes/ no /unclear	hand	none	lateral	2	4/40; 3/36; 1 day		
		no/ no/ no	hand	none	lateral	2	33/102; 55/113; 1 day		
Al-Negrish & Habahbeh 2006 [22]	120 adults or adolescents	yes/ no/ no	hand	calcium hydroxide	lateral	2	8/54; 14/58; 2 days	1/54; 3/58; 7 days	
DiRenzo 2002 [23]	80 adults	both/ yes/ unclear	rotary	none	lateral	2	-/39; -/33; 1 day no significant difference on continuous scale		
Dorsani 2013 [24]	57 adults	no/ unclear/ yes	rotary	calcium hydroxide	lateral	2			10/24; 6/22; 1 year
Fava 1989 [25]	48 adults and children	no/ no/ unclear	hand	phenole	lateral	2	1/30; 0/30; 2 days		
Fava 1994 [26]	52 adults or adolescents	yes/ yes/ unclear	hand	calcium hydroxide	lateral	n.g.	2/30; 1/30; 1 day		
Gesi 2006 [28]	256 adults	yes/ both/ no	hand	calcium hydroxide	lateral	2	16/130; 18/126; 7 days		9/123; 8/121; 3 years
Ghoddusi 2006 [27]	60 adults	no/ both/ yes	hand	calcium hydroxide	lateral	2	1/20; 8/20; 3 days	7/20; 0/20; 3 days	
Ince 2009 [29]	306 adults	yes/ both/ no	hand	none	lateral	2	19/87; 16/66; 3 days		
		no/ both/ mixed	hand	none	lateral	2	9/66; 14/87; 3 days		
Jabeen 2014 [30]	120 adults or adolescents	no/ no/ no	unclear	calcium hydroxide	lateral	2	23/60; 11/60; 1day		
Liu & Leng 2013 [31]	143 adults	no/ unclear/ mixed	unclear	cortisomal	lateral	2-3	52/95; 28/48; 1 day		10/87; 4/42; 1 year
Molander 2007 [32]	94 adults	no/ no/ yes	rotary	calcium hydroxide	lateral	2			17/49; 10/40; 2 years
Mulhern 1982 [33]	60 adults or adolescents	no/ no/ mixed	hand	none	lateral	3	7/30; 6/30; 2 days		
Oginni 2004 [34]	255 adults	both/ both/ mixed	unclear	unclear	lateral	n.g.	58/107; 61/136; 1 day	19/104; 10/123; 7 days	
Paredes-Vieyra 2012 [35]	287 adults	no/ no/ yes	rotary	calcium hydroxide	lateral	2			5/146; 15/136; 2 years
Pekruhn 1981 [36]	102 cases of unclear age	unclear/ unclear/ unclear	hand	formocresol	vertical	2	8/51; 8/51; 1 day		
Penesis 2008 [37]	97 adults	no/ unclear/ yes	rotary	calcium hydroxide+ CHX	vertical	2			7/35; 7/31; 2 years
Peters and Wesslink 2002 [38]	39 adults	no/ no/ yes	hand	calcium hydroxide	lateral	2			0/21; 1/17; 4.5 years
Prashanth 2011 [39]	32 adults	no/ unclear/ yes	rotary	unclear	vertical	2	1/8; 0/8; 2 days		
		yes/ unclear/ no	rotary	unclear	vertical	2	1/8; 1/8; 2 days		
Rao 2014	148 adults	no/	rotary	none	lateral	2	-/74; -/74 1 day		

[40]		unclear/ unclear					no significant difference on continuous scale		
Risso 2008 [41]	118 adolescents	no/ both/ mixed	hand	calcium hydroxide	lateral	2	-/57;-/61;1 day results not reported	1/57;1/61; 10 days	
Singh and Kargh 2012 [42]	200 adults	both/ unclear/ no	rotary	none	lateral	2	-/94; -/94; 1 day no significant difference on continuous scale	0/9; 0/94; 6 days	
Trope 1999 [44], Waltimo 2005 [43]	81 adults	no/ unclear/ yes	hand	calcium hydroxide	lateral	2			9/45; 6/31; 1 year
Wang 2010 [45]	100 adults	yes/ yes/ no	rotary	calcium hydroxide	lateral	2	28/43; 27/46; 1 day	1/43; 1/46; 7 days	
Weiger 2000 [46]	73 adults or adolescents	no/ both/ yes	hand	calcium hydroxide	lateral	n.g.			3/36; 2/31; up to 5 years
Wong 2015a [47]	567 adults	both/ both/ mixed	rotary	calcium hydroxide	lateral or core carrier	2	68/275; 88/263; 1 day		
Wong 2015b [8]	228 adults	both/ both/ mixed	rotary	calcium hydroxide	core carrier	2-3	25/117; 12/103; 7 days		13/117; 13/103; 2 years
Yoldas 2004 [48]	218 adults	no/ both/ re-treatment	both	calcium hydroxide + CHX	lateral	2	44/106; 32/112; 7 days	8/106; 2/112; 7 days	

Abbreviations: CHX chlorhexidine, n.g. not given, obtur. obturation

Six trials treated only teeth with vital pulps, six treated vital and non-vital teeth or did not specify vitality; the remaining trials treated non-vital teeth. Three trials clearly stated to treat only teeth with preoperative pain, 15 treated both painful and painless teeth or did not state any details on preoperative symptoms, the remaining trials treated only teeth without preoperative symptoms. Ten trials included only teeth with peri-apical lesions, 13 trials did not report on radiographic status of the peri-apex or treated both teeth with and without lesions; the remaining trials treated only teeth without any detectable lesions.

Six trials were found to have low risk of bias (Tab. S2), the remaining trials showed high or unclear overall risk of bias. This was mainly due to a lack of examiner blinding or allocation concealment. Two trials did not at all report on randomization, and were treated accordingly in the performed meta-analysis. The majority of trials mentioned randomization, but did not state how sequences were generated. Attrition was generally limited (as most trials did only assess short-term pain, see below), as was risk of selective reporting.

Risk of long-term complications

Long-term complications were investigated by ten trials, with a total of 1257 teeth being treated. Mean follow-up was 2.3 years (range: 1-5 years). All trials had used calcium hydroxide as medication in the multiple-visit group. All but two trials had high risk of bias. Risk of complications was not significantly different in single- versus multiple-visit treatment (RR: 1.00 [95% CI: 0.75/1.35]). Heterogeneity was low. Publication bias was not detected via Egger's test (p=0.36) or funnel plot analysis (Fig. 2a, Appendix Fig. S1a).

Preoperative conditions were not found to significantly impact on effect estimates (Tab. 2).

Table 2: Meta-regression analysis. LogRR and 95% CI are given to allow comparing relative effect estimates between subgroups of treatments. n: number of studies; n/a not available (as all studies used calcium hydroxide).

	Outcomes		
Subgroups	**Long-term complications (n=10)**	**Any postoperative pain (n=23)**	**Postoperative flare-up (n=8)**
Pain-free versus painful teeth	-0.33 (-1.47/1.14)	0.15 (-0.50/0.80)	1.10 (-2.44/4.63)
Vital versus non-vital teeth	0.10 (-0.90/1.10)	-0.02 (-0.60/0.58)	-0.08 (-2.26/2.10)
Teeth with peri-apical lesions versus teeth without lesions	-0.13 (-1.22/0.98)	-1.18 (-2.91/0.55)	0.79 (-0.87/2.46)
Calcium hydroxide medication versus no medication	n/a	0.11 (-0.27/0.50)	-0.27 (-1.29/0.74)

Studies which did not state to have randomly allocated treatments did not find significantly different risk ratios (p=0.35). Using TSA, we found neither the conventional thresholds for benefit or harm nor the TSMB for benefit, harm or futility to be reached. Sample size was far below DARIS (Fig. 2b). Given that risk of bias was serious and the number of events low (leading to imprecision), our confidence in this finding was weak.

Risk of experiencing any postoperative pain

20 studies used binary estimates to express risk of short-term pain. Of these, three had used a factorial design, with resulting subgroups being handled as independent studies. Three further studies used visual-analogue scales and reported pain to not be significantly different; these were included in a sensitivity analyses. For the base-case analysis, a total of 3008 teeth were available and assessed. Pain had been recorded after a mean of 2 days (range: 1-7 days) postoperatively. Three trials had compared pain only after instrumentation, the other studies compared pain after obturation. All but three trials showed high risk of bias.

Risk of pain was not significantly different in single- versus multiple-visit treatment (RR: 0.99 [95% CI: 0.76/1.30]). Heterogeneity was moderate. There was no indication for publication bias via Egger's test (p=0.46) or funnel plot analysis (Fig. 3a, Appendix Fig. S1b). Preoperative conditions or the use of a calcium hydroxide instead of no root-canal medication between visits had no significant impact on effect estimates (Tab. 2). Studies which did not state to have randomly allocated treatments did not find significantly different risk ratios compared with studies which had clearly stated randomization (p=0.46). Including imputed studies which had only reported that differences between groups were non-significant (but had not given an effect estimate) increased the total number of assessed teeth to 3417, but did not significantly change our estimates (RR=1.00 [0.86/1.21]). Excluding those trials which only reported on pain after instrumentation, not obturation, also had no significant impact (RR=0.99 [0.84/1.17]). Using TSA, we found the conventional thresholds for benefit to be spuriously crossed, while the TSMB for benefit was not reached. Futility boundaries were not constructible due to too few data being available. The sample size was far below DARIS (Fig. 3b). Given the serious risk of bias, but only limited evidence for imprecision, this finding is supported by moderate evidence according to GRADE.

Risk of flare-up

Risk of flare-up was recorded by eight studies. A total of 1110 teeth had been followed over a period of 7-10 days. All studies stated to be randomized trials, two studies showed low, the rest high risk of bias.

Risk of flare-up was significantly higher after single- versus multiple-visit treatment (RR: 2.13 [95% CI: 1.16/3.89]). Heterogeneity was low. There was some indication for publication bias based on funnel plot analysis, but not Egger's test (p=0.26). Adjusting the estimate accordingly increased the RR (Fig. 4a, Appendix Fig. S1c). Preoperative conditions and the root-canal medication had no significant impact on effect estimates (Tab. 2). Using TSA, we found the conventional thresholds for harm to be spuriously crossed, while the TSMB for harm was not reached. Futility boundaries were not constructible due to too few data being available. The sample size was far below DARIS (Fig. 4b). Given the serious risk of bias, imprecision and publication bias being present, our confidence in this finding is supported by only very weak evidence according to GRADE.

Discussion

Even after optimal root-canal disinfection via instrumentation and irrigation, bacteria usually remain within the root-canal system.[49 50] During multiple-visit root-canal treatment, an antibacterial medication like calcium hydroxide is placed in the root-canals, thereby aiming to further disinfect the canals between treatment appointments, the efficacy of which remains unclear at present.[49 51-53] In contrast, in single-visit root-canal treatment any further appointments and intra-canal medications are omitted, and the root-canal system obturated directly after instrumentation and irrigation, aiming to seal remaining bacteria and deprive them from both space and nutrition.[3 46 54 55]

For risk of long-term complications, we did not find a difference between single and multiple visit endodontic treatment. This was our primary outcome, as such complications oftentimes decide the fate of the tooth.[56-58] It is noteworthy that this was supported by a range of studies (i.e. studies with high or low risk, small or large samples, in adults or adolescents, vital or non-vital teeth, teeth with or without peri-apical lesions) with relatively homogenous findings. Only one trial found significant differences between groups (favoring single-visit treatment),[35] all others did not find one treatment significantly superior over the other.

Based on our analyses, the discussed confounders do not seem to significantly affect the relative risk of complications. Even in teeth with peri-apical lesions, single-visit treatment showed no significantly different risk of complications. This finding is in line with that from a previous review.[6] We want to highlight that our performed meta-regression and subgroup analyses are potentially underpowered, with high risk of type II errors. In general, our findings on the risk of complications outcome are supported by limited data, as indicated by TSA. Based on this analysis, no firm evidence on benefit, harm or futility is available (while the cumulative Z-curve never crossed any threshold for significance, once more confirming a trend towards non-difference of treatments).

The resulting evidence was graded as weak, mainly due to risk of bias of trials. Thus, a number of recommendations towards future studies need to be made: First, future trials should have higher internal validity, e.g. by performing and reporting on sequence generation, by sufficiently concealing the allocation, and by blinding assessors, all to reduce the risk of selection and detection bias. We are well aware that blinding operators or patients is impossible in such trials; future reviews should reflect on this when assessing risk of bias (as we did accordingly). Second, trials should be performed in realistic (primary care) settings with sufficiently long follow-up periods, as complications are expected to occur long-term. Third, trials should aim to investigate the relevance of preoperative conditions as possible confounders, as current data are insufficient to conclude on the suitability of single- versus multiple-visit treatment in different teeth or patients.

We also found single-visit treatment to not significantly increase the risk of short-term postoperative pain, which is in line with findings from previous reviews.[3 6 59] Pain is a relevant outcome, despite being reported only for brief periods after treatment and not being a strong predictor for success,[50] as it is directly burdening patients and could influence their attitude and behavior towards future endodontic treatment. Our findings were again relatively consistent between trials regardless of their risk of bias, setting, patients or treated teeth. Only three studies found significant differences between groups; two in favor of single-

visit treatment,[21 27] one in favor of multiple-visit treatment.[30] All three were performed in non-vital teeth. It is again important to note that while we did not identify significant confounders (which is in line with previous findings),[60] our meta-regression analyses are (as discussed) of limited power. However, the overall number of treated teeth was relatively high, and while current data was insufficient to establish firm evidence, we expect futility boundaries of TSA to be reached if future trials confirm these findings. Given the discussed uncertainties associated with the preoperative condition (vitality, symptoms), researchers should account for these confounders when designing and evaluating future trials in the field.

We found single-visit treatment to significantly increase the risk of flare-up, which is in agreement with a previously identified increased risk of swelling after single-visit treatment.[3] It should be highlighted that our analysis for this outcome was built on only few, mainly high risk trials, and that one particular study contributed a lot to the effect estimate given its weighting.[34] This weighting was the result of the high incidence of flare-up in this study (20% in the single-visit group), which is much higher than that in all other trials. Excluding this study from the analysis decreased the effect estimates, with no significant difference between groups remaining (RR: 1.85 [0.89/3.86]). Given that TSA indicated that no firm evidence has been reached so far, caution is thus required when interpreting our finding regarding flare-up. Such caution is further justified as flare-ups occurring directly after treatment as well as up to 7 days after instrumentation (or obturation) were pooled. Moreover, risk of flare-ups might be affected by further factors like patients' age, gender or systemic conditions. While patients with systemic conditions were excluded in all studies, insufficient information was available regarding gender and age distribution. Future studies should report in more detail on these aspects.

This review has a number of limitations. First, it builds only on randomized or at least controlled trials. While we see the value of practice-based long-term cohort studies (which have higher external validity and yield findings in a more relevant timeframe), we actively

restricted our review on controlled studies to minimize the risk of selection bias, the impact of which can be expected to be potentially severe given that treatment decisions might be made based on the preoperative condition of the tooth. For example, dentists might be more willing to perform single-visit treatment in vital teeth, or molars might be treated in multiple visits more often due to practical reasons. This would greatly distort the true relative efficacy of both therapies.

Second, our primary outcome, complications, is a composite of different components like long-term pain, clinical signs of inflammation and infection (swelling, sinus track formation), and radiographic success (which does not need the patient to experience symptoms). For each component, a decision to re-treat or not might differ depending on who is deciding: Dentists (and researchers specializing in endodontics) might see a persistent peri-apical lesion as an indication to re-treat even in the absence of symptoms (anticipating such symptoms to occur at some stage in the future, with poorer prognosis for re-treatments). In contrast, patients might not be willing to re-treat such tooth (which might as well be justified when considering the success rates of the available re-treatments and the resulting treatment costs).[58]

Third, one of our secondary outcomes, the risk of experiencing any postoperative pain, does not account for the degree of pain, losing a significant amount of information. That was done as most trials reported pain using either a binary scales (pain yes/no) or ordinal scales, which did not always use identical categories and pose great difficulties when pooling them (or require the definition of a certain pain threshold, which is usually arbitrary). Future studies should use continuous outcome measures like visual analogues scales, allowing to fully display the recorded information on pain. It is noteworthy that those studies which used such scales also found no significant difference of pain levels between treatments.

Last, most included trials reported only on very limited periods after treatment. While this might be acceptable for short-term pain, a follow-up of mean 2.3 years is insufficient to truly

reflect “long-term” complications (as is applied definition of minimum one year follow-up to consider a complication as long-term). This is closely related with the discussed limitations of randomized trials, which are seldom able to follow-up teeth for much longer given the high associated efforts and costs.

Future trials are thus needed to gain firm evidence whether differences in outcomes between single or multiple visit root-canal treatment exist. To improve validity and comparability, these trials should aim for standardized outcome measures (e.g. visual analogue scale for pain assessment; agreed definition for success/failure), long-term follow-up periods and limited risk of bias (while certain bias cannot be fully excluded). They should best be performed in representative settings and populations and report in detail on confounders of treatment success.

In conclusion and within the limitations of this review, dentists can provide root-canal treatment in one or multiple visits. Further recommendations towards when to prefer one treatment over the other are currently not available. Given the possibly increased risk of flare-up, a careful recommendation could be to prefer multiple-visit treatment in teeth where the risk if complication is increased (e.g. teeth with existing peri-apical lesions). Clinical decisions should be made with practical aspects (like scheduling of patients) and patients’ and dentists’ preferences in mind.

Figure Legends

Figure 1: Study flow. Database screening was performed using a four-pronged search strategy, combining four domains of the search using Boolean operators. Number of studies yielded in Medline by each search domain are shown in the upper boxes; combining these boxes led to the number of results as shown for each database.

Figure 2: Risk of long-term complications after single- versus multiple-visit root-canal treatment. (a) Forest plot, with Risk Ratio (RR) and 95% confidence intervals (CI) per study and overall (black diamond) being given. Heterogeneity across studies is indicated by I^2 and Q. Low risk of bias and lack of random allocation of treatment is indicated by asterisks and hashtag. (b) Trial sequential analysis. The cumulative Z-score (black), i.e., the accumulated level of significance, was plotted against the number of participants (N) accrued, which was compared with the diversity-adjusted required information size (DARIS). The Z-curve does not cross the conventional thresholds for superiority or inferiority (hatched grey lines). Neither the DARIS nor TSMB (grey solid lines) were reached. The information fraction was too small to draw trial sequential futility boundaries.

Figure 3: Risk of experiencing any postoperative pain after single- versus multiple-visit root-canal treatment. (a) Forest plot. Low risk of bias and lack of random allocation of treatment is indicated by asterisks and hashtag. Studies which compared treatments in different subgroup of teeth were handled as independent studies and are indicated accordingly. (b) Trial sequential analysis. The information fraction was too small to draw trial sequential futility boundaries.

Figure 4: Risk of experiencing flare-up after single- versus multiple-visit root-canal treatment. (a) Forest plot. RR and 95% CI were adjusted for publication bias using trim-and-fill (RRa). Low risk of bias and lack of random allocation of treatment is indicated by asterisks and hashtag. Studies which compared treatments in different subgroup of teeth were handled as independent studies and are indicated accordingly. (b) Trial sequential analysis. The information fraction was too small to draw trial sequential futility boundaries.

Contributorship statement

F. Schwendicke, contributed to conception, design, data acquisition, analysis, and interpretation, drafted and critically revised the manuscript; G. Göstemeyer, contributed to conception, design, data acquisition, interpretation and critically revised the manuscript.

Competing interests

The authors declare there is no conflict of interest

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No additional data are available.

References

1. Glennon JP, Ng YL, Setchell DJ, et al. Prevalence of and factors affecting postpreparation pain in patients undergoing two-visit root canal treatment. International endodontic journal 2004;**37**(1):29-37
2. Ng YL, Glennon JP, Setchell DJ, et al. Prevalence of and factors affecting post-obturation pain in patients undergoing root canal treatment. International endodontic journal 2004;**37**(6):381-91 doi: 10.1111/j.1365-2591.2004.00820.x[published Online First: Epub Date]|.
3. Figini L, Lodi G, Gorni F, et al. Single versus multiple visits for endodontic treatment of permanent teeth. The Cochrane database of systematic reviews 2007(4):Cd005296 doi: 10.1002/14651858.CD005296.pub2[published Online First: Epub Date]|.
4. Ng YL, Mann V, Rahbaran S, et al. Outcome of primary root canal treatment: systematic review of the literature – Part 2. Influence of clinical factors. International endodontic journal 2008;**41**(1):6-31 doi: 10.1111/j.1365-2591.2007.01323.x[published Online First: Epub Date]|.
5. Raju TB, Seshadri A, Vamsipavani B, et al. Evaluation of pain in single and multi rooted teeth treated in single visit endodontic therapy. Journal of international oral health : JIOH 2014;**6**(1):27-32
6. Su Y, Wang C, Ye L. Healing rate and post-obturation pain of single- versus multiple-visit endodontic treatment for infected root canals: a systematic review. Journal of endodontics 2011;**37**(2):125-32 doi: 10.1016/j.joen.2010.09.005[published Online First: Epub Date]|.
7. De-Deus G, Canabarro A. Strength of recommendation for single-visit root canal treatment: grading the body of the evidence using a patient-centered approach. International endodontic journal 2016 doi: 10.1111/iej.12621[published Online First: Epub Date]|.
8. Wong AW, Tsang CS, Zhang S, et al. Treatment outcomes of single-visit versus multiple-visit non-surgical endodontic therapy: a randomised clinical trial. BMC oral health 2015;**15**(1):162 doi: 10.1186/s12903-015-0148-x[published Online First: Epub Date]|.
9. American Association of Endodontists. Glossary of endodontic terms. 7th edition. Secondary Glossary of endodontic terms. 7th edition. 2003.
10. Masood M, Masood Y, Newton JT. The clustering effects of surfaces within the tooth and teeth within individuals. Journal of dental research 2015;**94**(2):281-8 doi: 10.1177/0022034514559408[published Online First: Epub Date]|.
11. Higgins JPT, Thompson SG. Quantifying heterogeneity in a meta-analysis. Statistics in medicine 2002;**21**(11):1539-58 doi: 10.1002/sim.1186[published Online First: Epub Date]|.
12. Egger M, Smith GD, Schneider M, et al. Bias in meta-analysis detected by a simple, graphical test. BMJ 1997;**315**(7109):629-34 doi: 10.1136/bmj.315.7109.629[published Online First: Epub Date]|.

13. Higgins JPT, Green S, editors. *Cochrane Handbook for Systematic Reviews of Interventions*. Version 5.10 (updated March 2011): The Cochrane Collaboration, 2011.
14. Duval S, Tweedie R. Trim and fill: A simple funnel-plot-based method of testing and adjusting for publication bias in meta-analysis. Biometrics 2000;**56**(2):455-63
15. Wetterslev J, Thorlund K, Brok J, et al. Trial sequential analysis may establish when firm evidence is reached in cumulative meta-analysis. J Clin Epidemiol 2008;**61**(1):64-75 doi: 10.1016/j.jclinepi.2007.03.013[published Online First: Epub Date]|.
16. Thorlund K, Engstrøm J, Wetterslev J, et al. User Manual for Trial Sequential Analysis (TSA). http://www.ctu.dk/tsa/files/tsa_manual.pdf 2011:1-115
17. Schwendicke F, Goestemeyer G, Gluud C. Cavity lining after excavating caries lesions: meta-analysis and trial sequential analysis of randomized clinical trials. Journal of Dentistry 2015;**doi: 10.1016/j.jdent.2015.07.017**
18. Atkins D, Best D, Briss PA, et al. Grading quality of evidence and strength of recommendations. BMJ 2004;**328**(7454):1490
19. Andrews J, Guyatt G, Oxman AD, et al. GRADE guidelines: 14. Going from evidence to recommendations: the significance and presentation of recommendations. J Clin Epidemiol 2013;**66**(7):719-25 doi: 10.1016/j.jclinepi.2012.03.013[published Online First: Epub Date]|.
20. Akbar I, Iqbal A, Al-Omiri MK. Flare-up rate in molars with periapical radiolucency in one-visit vs two-visit endodontic treatment. The journal of contemporary dental practice 2013;**14**(3):414-8
21. Albashaireh ZS, Alnegrish AS. Postobturation pain after single- and multiple-visit endodontic therapy. A prospective study. Journal of dentistry 1998;**26**(3):227-32
22. Al-Negrish AR, Habahbeh R. Flare up rate related to root canal treatment of asymptomatic pulpally necrotic central incisor teeth in patients attending a military hospital. Journal of dentistry 2006;**34**(9):635-40 doi: 10.1016/j.jdent.2005.12.007[published Online First: Epub Date]|.
23. DiRenzo A, Gresla T, Johnson BR, et al. Postoperative pain after 1- and 2-visit root canal therapy. Oral surgery, oral medicine, oral pathology, oral radiology, and endodontics 2002;**93**(5):605-10
24. Dorasani G, Madhusudhana K, Chinni SK. Clinical and radiographic evaluation of single-visit and multi-visit endodontic treatment of teeth with periapical pathology: An in vivo study. Journal of conservative dentistry : JCD 2013;**16**(6):484-8 doi: 10.4103/0972-0707.120933[published Online First: Epub Date]|.
25. Fava LR. A comparison of one versus two appointment endodontic therapy in teeth with non-vital pulps. International endodontic journal 1989;**22**(4):179-83
26. Fava LR. A clinical evaluation of one and two-appointment root canal therapy using calcium hydroxide. International endodontic journal 1994;**27**(1):47-51
27. Ghoddusi J, Javidi M, Zarrabi MH, et al. Flare-ups incidence and severity after using calcium hydroxide as intracanal dressing. The New York state dental journal 2006;**72**(4):24-8
28. Gesi A, Hakeberg M, Warfvinge J, et al. Incidence of periapical lesions and clinical symptoms after pulpectomy--a clinical and radiographic evaluation of 1- versus 2-session treatment. Oral surgery, oral medicine, oral pathology, oral radiology, and endodontics 2006;**101**(3):379-88 doi: 10.1016/j.tripleo.2005.05.073[published Online First: Epub Date]|.

29. Ince B, Ercan E, Dalli M, et al. Incidence of postoperative pain after single- and multi-visit endodontic treatment in teeth with vital and non-vital pulp. European journal of dentistry 2009;**3**(4):273-9
30. Jabeen S, Khurshiduzzaman M. Incidence of post obturation pain following single and multi visit root canal treatment in a teaching hospital of Bangladesh. Mymensingh medical journal : MMJ 2014;**23**(2):254-60
31. Liu S, Leng Z-y. Short-term clinical effect of single-visit root-canal therapy in infected root canals. Journal of Shanghai Jisobong University 2013;**33**(7):1014-17
32. Molander A, Warfvinge J, Reit C, et al. Clinical and radiographic evaluation of one- and two-visit endodontic treatment of asymptomatic necrotic teeth with apical periodontitis: a randomized clinical trial. Journal of endodontics 2007;**33**(10):1145-8 doi: 10.1016/j.joen.2007.07.005[published Online First: Epub Date]|.
33. Mulhern JM, Patterson SS, Newton CW, et al. Incidence of postoperative pain after one-appointment endodontic treatment of asymptomatic pulpal necross in single-rooted teeth. Journal of endodontics 1982;**8**(8):370-5
34. Oginni A, Udoye CI. Endodontic flare-ups: comparison of incidence between single and multiple visits procedures in patients attending a Nigerian teaching hospital. Odonto-stomatologie tropicale = Tropical dental journal 2004;**27**(108):23-7
35. Paredes-Vieyra J, Enriquez FJ. Success rate of single- versus two-visit root canal treatment of teeth with apical periodontitis: a randomized controlled trial. Journal of endodontics 2012;**38**(9):1164-9 doi: 10.1016/j.joen.2012.05.021[published Online First: Epub Date]|.
36. Pekruhn RB. Single-visit endodontic therapy: a preliminary clinical study. Journal of the American Dental Association (1939) 1981;**103**(6):875-7
37. Penesis VA, Fitzgerald PI, Fayad MI, et al. Outcome of one-visit and two-visit endodontic treatment of necrotic teeth with apical periodontitis: a randomized controlled trial with one-year evaluation. Journal of endodontics 2008;**34**(3):251-7 doi: 10.1016/j.joen.2007.12.015[published Online First: Epub Date]|.
38. Peters LB, Wesselink PR. Periapical healing of endodontically treated teeth in one and two visits obturated in the presence or absence of detectable microorganisms. International endodontic journal 2002;**35**(8):660-7
39. Prashanth MB, Tavane PN, Abraham S, et al. Comparative evaluation of pain, tenderness and swelling followed by radiographic evaluation of periapical changes at various intervals of time following single and multiple visit endodontic therapy: an in vivo study. The journal of contemporary dental practice 2011;**12**(3):187-91
40. Rao KN, Kandaswamy R, Umashetty G, et al. Post-Obturation pain following one-visit and two-visit root canal treatment in necrotic anterior teeth. Journal of international oral health : JIOH 2014;**6**(2):28-32
41. Risso PA, Cunha AJ, Araujo MC, et al. Postobturation pain and associated factors in adolescent patients undergoing one- and two-visit root canal treatment. Journal of dentistry 2008;**36**(11):928-34 doi: 10.1016/j.jdent.2008.07.006[published Online First: Epub Date]|.
42. Singh S, Garg A. Incidence of post-operative pain after single visit and multiple visit root canal treatment: A randomized controlled trial. Journal of conservative dentistry : JCD 2012;**15**(4):323-7 doi: 10.4103/0972-0707.101888[published Online First: Epub Date]|.

43. Waltimo T, Trope M, Haapasalo M, et al. Clinical efficacy of treatment procedures in endodontic infection control and one year follow-up of periapical healing. Journal of endodontics 2005;**31**(12):863-6
44. Trope M, Delano EO, Orstavik D. Endodontic treatment of teeth with apical periodontitis: single vs. multivisit treatment. Journal of endodontics 1999;**25**(5):345-50 doi: 10.1016/s0099-2399(06)81169-6[published Online First: Epub Date]|.
45. Wang C, Xu P, Ren L, et al. Comparison of post-obturation pain experience following one-visit and two-visit root canal treatment on teeth with vital pulps: a randomized controlled trial. International endodontic journal 2010;**43**(8):692-7 doi: 10.1111/j.1365-2591.2010.01748.x[published Online First: Epub Date]|.
46. Weiger R, Rosendahl R, Lost C. Influence of calcium hydroxide intracanal dressings on the prognosis of teeth with endodontically induced periapical lesions. International endodontic journal 2000;**33**(3):219-26
47. Wong AW, Zhang S, Li SK, et al. Incidence of post-obturation pain after single-visit versus multiple-visit non-surgical endodontic treatments. BMC oral health 2015;**15**:96 doi: 10.1186/s12903-015-0082-y[published Online First: Epub Date]|.
48. Yoldas O, Topuz A, Isci AS, et al. Postoperative pain after endodontic retreatment: single- versus two-visit treatment. Oral surgery, oral medicine, oral pathology, oral radiology, and endodontics 2004;**98**(4):483-7 doi: 10.1016/s1079210404002161[published Online First: Epub Date]|.
49. Bystrom A, Sundqvist G. Bacteriologic evaluation of the efficacy of mechanical root canal instrumentation in endodontic therapy. Scandinavian journal of dental research 1981;**89**(4):321-8
50. Sjogren U, Figdor D, Persson S, et al. Influence of infection at the time of root filling on the outcome of endodontic treatment of teeth with apical periodontitis. International endodontic journal 1997;**30**(5):297-306
51. Han GY, Park SH, Yoon TC. Antimicrobial activity of Ca(OH)2 containing pastes with Enterococcus faecalis in vitro. Journal of endodontics 2001;**27**(5):328-32 doi: 10.1097/00004770-200105000-00004[published Online First: Epub Date]|.
52. Siqueira JF, Jr., Lopes HP, de Uzeda M. Recontamination of coronally unsealed root canals medicated with camphorated paramonochlorophenol or calcium hydroxide pastes after saliva challenge. Journal of endodontics 1998;**24**(1):11-4 doi: 10.1016/s0099-2399(98)80204-5[published Online First: Epub Date]|.
53. DiFiore PM, Peters DD, Setterstrom JA, et al. The antibacterial effects of calcium hydroxide apexification pastes on Streptococcus sanguis. Oral surgery, oral medicine, and oral pathology 1983;**55**(1):91-4
54. Soltanoff W. A comparative study of the single-visit and the multiple-visit edodontic procedure. Journal of endodontics 1978;**4**(9):278-81
55. Oliet S. Single-visit endodontics: a clinical study. Journal of endodontics 1983;**9**(4):147-52 doi: 10.1016/s0099-2399(83)80036-3[published Online First: Epub Date]|.
56. Ng YL, Mann V, Gulabivala K. Outcome of secondary root canal treatment: a systematic review of the literature. International endodontic journal 2008;**41**(12):1026-46 doi: 10.1111/j.1365-2591.2008.01484.x[published Online First: Epub Date]|.
57. Del Fabbro M, Taschieri S, Testori T, et al. Surgical versus non-surgical endodontic re-treatment for periradicular lesions. The Cochrane database of systematic reviews 2007(3):Cd005511 doi: 10.1002/14651858.CD005511.pub2[published Online First: Epub Date]|.

58. Schwendicke F, Stolpe M. Secondary Treatment for Asymptomatic Root Canal Treated Teeth: A Cost-effectiveness Analysis. Journal of endodontics 2015;**41**(6):812-6 doi: 10.1016/j.joen.2015.01.013[published Online First: Epub Date]|.
59. Wong AW, Zhang C, Chu CH. A systematic review of nonsurgical single-visit versus multiple-visit endodontic treatment. Clinical, cosmetic and investigational dentistry 2014;**6**:45-56 doi: 10.2147/ccide.s61487[published Online First: Epub Date]|.
60. Sathorn C, Parashos P, Messer H. The prevalence of postoperative pain and flare-up in single- and multiple-visit endodontic treatment: a systematic review. International endodontic journal 2008;**41**(2):91-9 doi: 10.1111/j.1365-2591.2007.01316.x[published Online First: Epub Date]|.

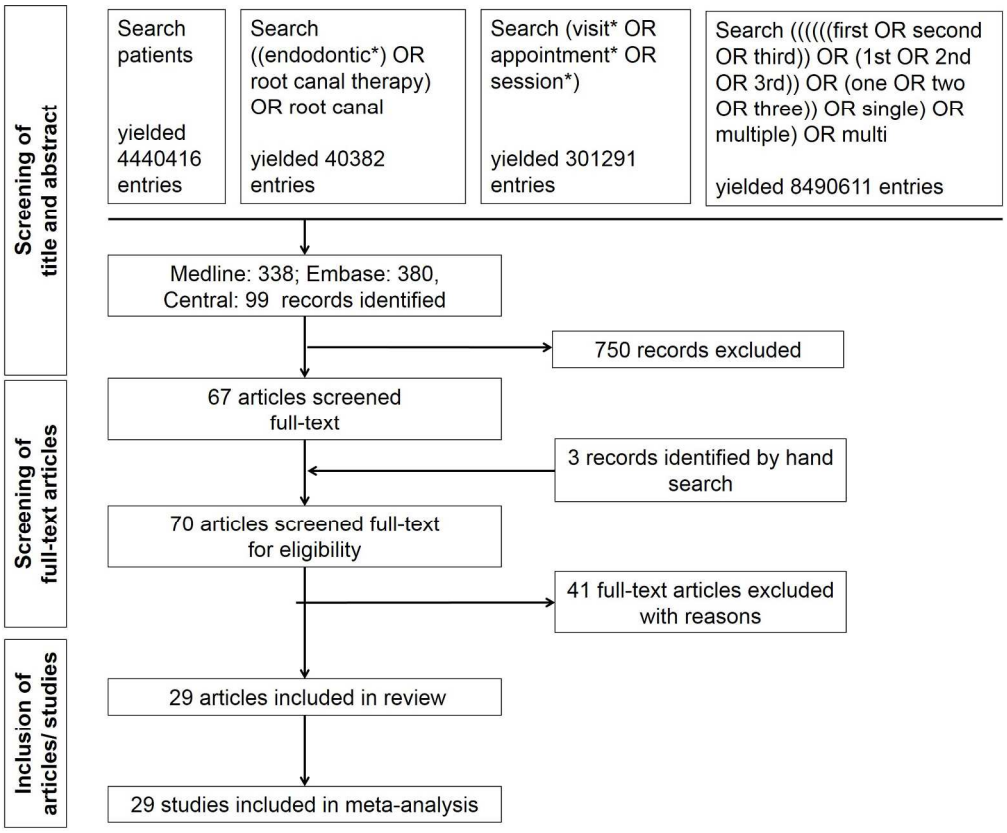

Figure 1: Study flow. Database screening was performed using a four-pronged search strategy, combining four domains of the search using Boolean operators. Number of studies yielded in Medline by each search domain are shown in the upper boxes; combining these boxes led to the number of results as shown for each database.

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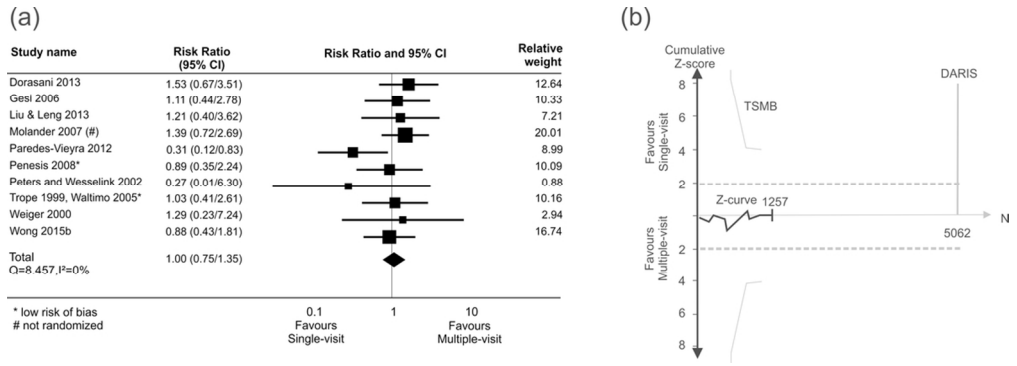

Figure 2: Risk of long-term complications after single- versus multiple-visit root-canal treatment. (a) Forest plot, with Risk Ratio (RR) and 95% confidence intervals (CI) per study and overall (black diamond) being given. Heterogeneity across studies is indicated by I^2 and Q. Low risk of bias and lack of random allocation of treatment is indicated by asterisks and hashtag. (b) Trial sequential analysis. The cumulative Z-score (black), i.e., the accumulated level of significance, was plotted against the number of participants (N) accrued, which was compared with the diversity-adjusted required information size (DARIS). The Z-curve does not cross the conventional thresholds for superiority or inferiority (hatched grey lines). Neither the DARIS nor TSMB (grey solid lines) were reached. The information fraction was too small to draw trial sequential futility boundaries.

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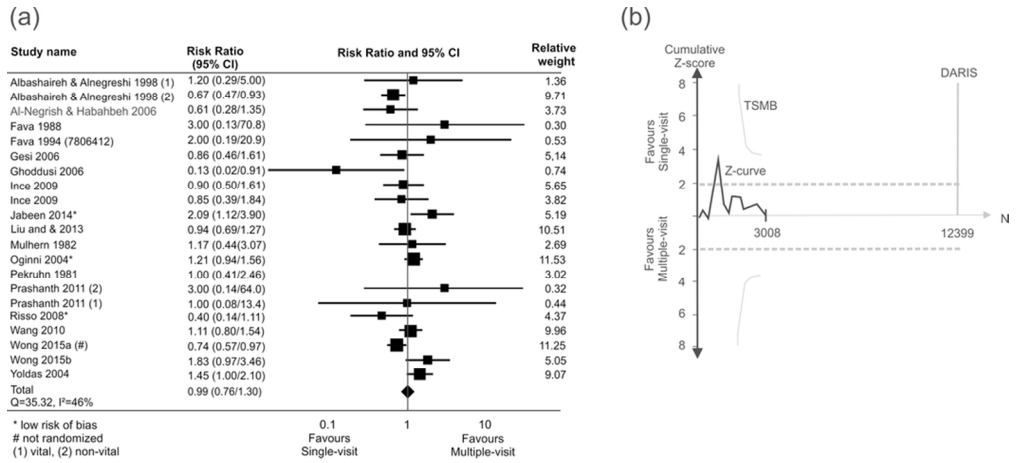

Figure 3: Risk of experiencing any postoperative pain after single- versus multiple-visit root-canal treatment. (a) Forest plot. Low risk of bias and lack of random allocation of treatment is indicated by asterisks and hashtag. Studies which compared treatments in different subgroup of teeth were handled as independent studies and are indicated accordingly. (b) Trial sequential analysis. The information fraction was too small to draw trial sequential futility boundaries.

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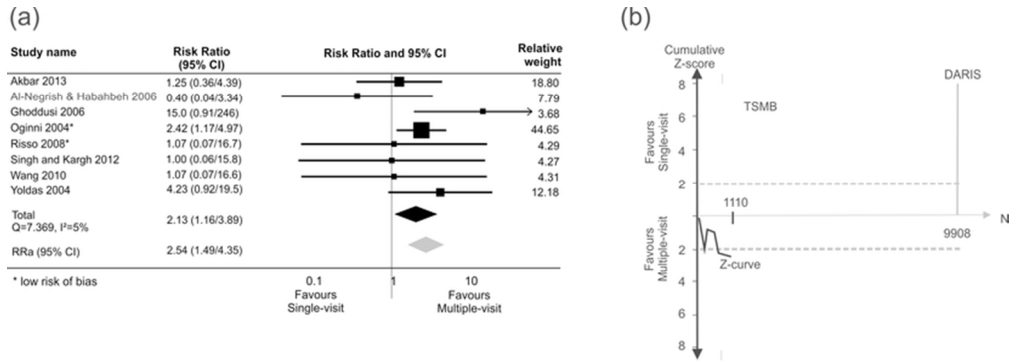

Figure 4: Risk of experiencing flare-up after single- versus multiple-visit root-canal treatment. (a) Forest plot. RR and 95% CI were adjusted for publication bias using trim-and-fill (RRa). Low risk of bias and lack of random allocation of treatment is indicated by asterisks and hashtag. Studies which compared treatments in different subgroup of teeth were handled as independent studies and are indicated accordingly. (b) Trial sequential analysis. The information fraction was too small to draw trial sequential futility boundaries.

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Appendix

Syntheses methods

Unit-of analysis issues were handled as follows: In studies reporting on more than two treatment groups, three approaches were taken to avoid unit-of-analysis conflicts: In case of groups being comparable, we combined them. If additional groups used treatments not in accordance with current standard (e.g. multiple-step treatment without any root-canal medication), this group was omitted. If a factorial design was used (e.g. both groups were compared in vital and non-vital teeth), with separate reporting for all groups, we compared subgroups and handled them as if they were separate studies for meta-analysis.

Meta-regression was additionally performed. As some studies did not clearly state randomization (see above), a sensitivity analysis excluding these studies was performed. Similarly, as some studies reported results to have not been significantly different (but did not report on exact effect estimates), we imputed the number of events per group as the mean event rate in a sensitivity analysis, making best use of all available information. For subgroup comparisons, Chi-square test was performed. For meta-regression, the unrestricted maximum-likelihood method was used; Bonferroni adjustment to correct for multiple testing was planned, but not required, as no significant associations were found even without such correction.

Trial sequential analysis was performed. RIS was calculated based on type I error risk of $\alpha=0.05$ and a type II error risk of $\beta=0.20$ (equivalent to a power of 0.80). The control event proportion (i.e. event incidence in multiple-visit group) and the relative risk reduction (RRR) were used to estimate RIS. RRR was based on an a priori defined worthwhile interventional effect of 20% (lower effects might be worthwhile, but would increase RIS even further) (1, 2). RIS was diversity (heterogeneity) adjusted (DARIS). To assess if differences yielded by conventional meta-analysis are robust, TSA additionally estimates trial sequential monitoring boundaries (TSMB), i.e. statistical thresholds for significance which are adapted depending on the so far reached sample size. The Lan-DeMets version (3) of the O'Brien–Fleming

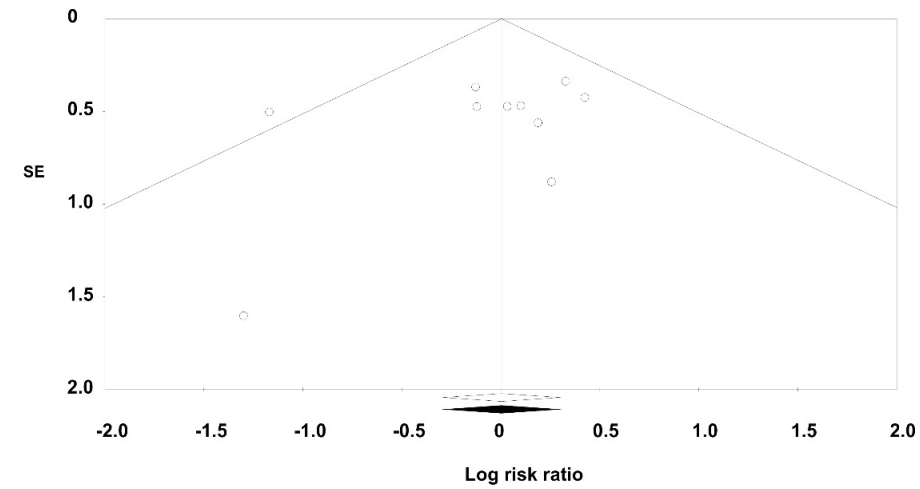
function (4) was used for calculating the TSMBs. In case the cumulative Z-value crossed the conventional boundary of significance (Z=±1.96) but not the TSMBs for benefit or harm, we defined such findings as spuriously significant. Firm evidence was assumed to be reached when the Z-curve crossed the TSMB for benefit or harm before the DARIS was reached. Effect estimates supported by only few small trials are thus handled stricter than those supported by large samples. In addition to such superiority/inferiority TSMBs, monitoring boundaries for futility were calculated (these indicate if further trial conduct is likely to be futile, i.e. if sufficient evidence has been accrued to claim non-inferiority of treatments). Further details regarding the applied method to calculate TSMB have been reported elsewhere (1). TSA was performed with TSA 0.9 (Copenhagen Trial Unit, Copenhagen, Denmark) (5).

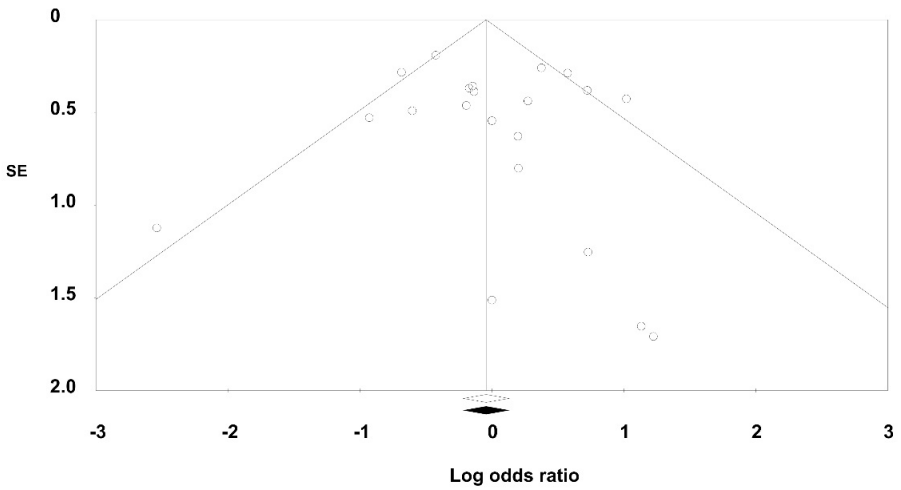
Table S1: Excluded Studies

Soltanoff 1978 (6)	Selection bias (allocation according to tooth status)
O'Keefe 1976 (7)	Selection bias (allocation according to available time)
ElMubarak 2010 (8)	No RCT
Raju 2014 (9)	Did not compare 1- vs 2 visits
Xavier 2013 (10)	No clinical outcome
Bhagwat 2013 (11)	Did not compare 1- vs 2 visits
Roane 1983 (12)	No RCT
Oliet 1983 (13)	Selection bias (allocation according to patient acceptance, available time, symptoms of tooth)
Ether 1978 (14)	Not available
Eleazer 1998 (15)	no RCT
Fava 1989 (16)	Compared different techniques
Fox 1970 (17)	Did not compare 1- vs 2 visits
Genet 1986 (18)	Did not compare 1- vs 2 visits
Morse 1987 (19)	Did not compare 1- vs 2 visits
Yesilsoy 1988 (20)	Did not compare 1- vs 2 visits
Trope 1991 (21)	Did not compare 1- vs 2 visits
Koba 1999 (22)	Did not compare 1- vs 2 visits
Glennon 2004 (23)	Did not compare 1- vs 2 visits
Ng 2004 (24)	no RCT
Georgopoulou 1986 (25)	no RCT
Jurcak 1993 (26)	no RCT
Imura 1995 (27)	no RCT
Walton 1992 (28)	no RCT
Alacam 1985 (29)	Did not compare 1- vs 2 visits
Torabinejad 1994 (30)	Did not compare 1- vs 2 visits
Sjögren 1990 (31)	Did not compare 1- vs 2 visits
Siqueira 2002 (32)	Did not compare 1- vs 2 visits
Orstavik 1996 (33)	Did not compare 1- vs 2 visits
Perkruhn 1986 (34)	Did not compare 1- vs 2 visits
Kvist 2004 (35)	no clinical outcomes reported (CFU)
Rudner 1981 (36)	no RCT
Kenrick 1999 (37)	no RCT
Sjögren 1997 (38)	Did not compare 1- vs 2 visits
Maddox 1977 (39)	Did not compare 1- vs 2 visits
Sjögren 1990 (31)	no RCT
Fleming 2010 (40)	no RCT
Singla 2008 (41)	pulpectomy
Kalhoro 2009 (42)	no RCT
Shaikh 2013 (43)	Not available

Table S2: Risk of bias of included studies. Bias assessment followed guidelines outline by The Cochrane Collaboration (44).

	Sequence generation	Allocation Concealment	Blinding of operator	Blinding of examiner	Incomplete data	Selective reporting	Overall risk of bias
Akbar 2013 (45)	Unclear	Unclear	High	Low	Low	Low	Unclear/High
Albashaireh & Alnegreshi 1998 (46)	Unclear	Unclear	High	Low	Low	Low	Unclear/High
Al-Negrish & Habahbeh 2006 (47)	Unclear	Unclear	High	High	Low	Low	Unclear/High
DiRenzo 2002 (48)	Low	Low	Low	Low	Low	Low	Low
Dorsani 2013 (49)	Unclear	Unclear	High	Low	Low	Low	Unclear/High
Fava 1989 (50)	Unclear	Unclear	High	Low	Low	Low	Unclear/High
Fava 1994 (51)	Unclear	Unclear	High	Low	Low	Low	Unclear/High
Gesi 2006 (52)	Low	Low	High	Low	Low	Low	Unclear/High
Ghoddusi 2006 (53)	Unclear	Unclear	High	Low	Low	Low	Unclear/High
Ince 2009 (54)	Unclear	Unclear	Unclear	Low	Low	Low	Unclear/High
Jabeen 2014 (55)	Low	Low	Low	Low	Low	Low	Low
Liu & Leng 2013 (56)	Unclear	Unclear	High	Low	Low	Low	Unclear/High
Molander 2007 (57)	High	Unclear	High	Low	Low	Low	Unclear/High
Mulhern 1982 (58)	Low	Low	High	Low	Low	Low	Unclear/High
Oginni 2004 (59)	Low	Low	Low	Low	Low	Low	Low
Paredes-Vieyra 2012 (60)	Unclear	High	High	Low	Low	Low	Unclear/High
Pekruhn 1981 (61)	Unclear	Unclear	Unclear	Low	Low	Low	Unclear/High
Penesis 2008 (62)	Low	Low	Low	Low	Low	Low	Low
Peters and Wesslink 2002 (63)	Low	Unclear	High	Low	Low	Low	Unclear/High
Prashanth 2011 (64)	Unclear	High	High	High	High	Low	Unclear/High
Rao 2014 (65)	Unclear	High	Low	Low	Low	Low	Unclear/High
Risso 2008 (66)	Low	Low	Low	Low	Low	Low	Low
Singh and Kargh 2012 (67)	Unclear	High	Low	Low	Low	Low	Unclear/High
Trope 1999 (68), Waltimo 2005 (69)	Low	Low	Low	Low	Low	Low	Low
Wang 2010 (70)	Low	Low	High	High	Low	Low	Unclear/High
Weiger 2000 (71)	Unclear	High	High	Low	Low	Low	Unclear/High
Wong 2015a (72)	High	High	Low	Low	Low	High	Unclear/High
Wong 2015b (73)	Low	Unclear	High	High	Low	Low	Unclear/High
Yoldas 2004 (74)	Unclear	Unclear	High	Low	Low	Low	Unclear/High





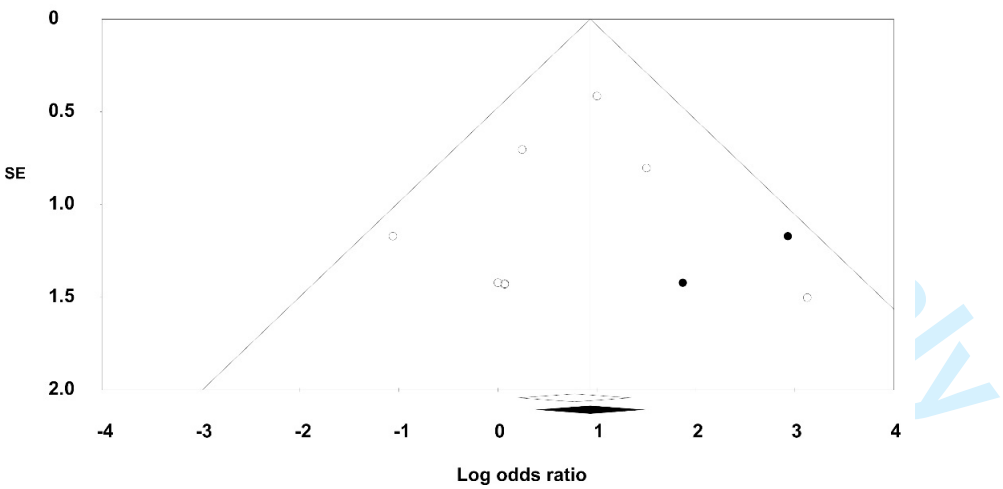


Figure S1: Funnel plots. (a) Risk long-term complications, (b) risk of experiencing any postoperative pain, (c) risk of experiencing a flare-up. Standard errors are plotted against logRR to estimate possible small study effects or publication bias via an asymmetry of the funnel. White circles: estimates reported by included studies, black balls: imputed estimates in case of suspected publication bias. White diamond: effect estimate based on included studies, black diamond: effect estimate based on included and imputed studies.

References for the appendix

1. Schwendicke F, Goestemeyer G, Gluud C. Cavity lining after excavating caries lesions: meta-analysis and trial sequential analysis of randomized clinical trials. *Journal of Dentistry* 2015;**doi: 10.1016/j.jdent.2015.07.017**.
2. Schwendicke F, Karimbux N, Allareddy V, Gluud C. Periodontal treatment for preventing adverse pregnancy outcomes: a meta- and trial sequential analysis. *PloS one* 2015;**10**(6):e0129060.
3. Demets DL, Lan KKG. Interim analysis: The alpha spending function approach. *Statistics in medicine* 1994;**13**(13-14):1341-52.
4. O'Brien PC, Fleming TR. A Multiple Testing Procedure for Clinical Trials. *Biometrics* 1979;**35**(3):549-56.
5. Thorlund K, Engstrøm J, Wetterslev J, Brok J, Imberger G, Gluud C. User Manual for Trial Sequential Analysis (TSA). http://www.ctu.dk/tsa/files/tsa_manual.pdf 2011:1-115.
6. Soltanoff W. A comparative study of the single-visit and the multiple-visit edodontic procedure. *Journal of endodontics* 1978;**4**(9):278-81.
7. O'Keefe EM. Pain in endodontic therapy: preliminary study. *Journal of endodontics* 1976;**2**(10):315-9.
8. El Mubarak AH, Abu-bakr NH, Ibrahim YE. Postoperative pain in multiple-visit and single-visit root canal treatment. *Journal of endodontics* 2010;**36**(1):36-9.
9. Raju TB, Seshadri A, Vamsipavani B, Abhilash K, Subhash AV, Kumari KV. Evaluation of pain in single and multi rooted teeth treated in single visit endodontic therapy. *Journal of international oral health : JIOH* 2014;**6**(1):27-32.
10. Xavier AC, Martinho FC, Chung A, Oliveira LD, Jorge AO, Valera MC, et al. One-visit versus two-visit root canal treatment: effectiveness in the removal of endotoxins and cultivable bacteria. *Journal of endodontics* 2013;**39**(8):959-64.
11. Bhagwat S, Mehta D. Incidence of post-operative pain following single visit endodontics in vital and non-vital teeth: An in vivo study. *Contemporary clinical dentistry* 2013;**4**(3):295-302.
12. Roane JB, Dryden JA, Grimes EW. Incidence of postoperative pain after single- and multiple-visit endodontic procedures. *Oral surgery, oral medicine, and oral pathology* 1983;**55**(1):68-72.
13. Oliet S. Single-visit endodontics: a clinical study. *Journal of endodontics* 1983;**9**(4):147-52.
14. al. ESe. A comparison of one and two visit endodontics. *J Farmacia Odontol* 1978(8):215.
15. Eleazer PD, Eleazer KR. Flare-up rate in pulpally necrotic molars in one-visit versus two-visit endodontic treatment. *Journal of endodontics* 1998;**24**(9):614-6.
16. Fava LR. One-appointment root canal treatment: incidence of postoperative pain using a modified double-flared technique. *International endodontic journal* 1991;**24**(5):258-62.
17. Fox J, Atkinson JS, Dinin AP, Greenfield E, Hechtman E, Reeman CA, et al. Incidence of pain following one-visit endodontic treatment. *Oral surgery, oral medicine, and oral pathology* 1970;**30**(1):123-30.
18. Genet JM, Wesselink PR, Thoden van Velzen SK. The incidence of preoperative and postoperative pain in endodontic therapy. *International endodontic journal* 1986;**19**(5):221-9.
19. Morse DR, Furst ML, Belott RM, Lefkowitz RD, Spritzer IB, Sideman BH. Infectious flare-ups and serious sequelae following endodontic treatment: a prospective randomized

trial on efficacy of antibiotic prophylaxis in cases of asymptomatic pulpal-periapical lesions. *Oral surgery, oral medicine, and oral pathology* 1987;**64**(1):96-109.
20. Yesilsoy C, Koren LZ, Morse DR, Rankow H, Bolanos OR, Furst ML. Post-endodontic obturation pain: a comparative evaluation. *Quintessence international* 1988;**19**(6):431-8.
21. Trope M. Flare-up rate of single-visit endodontics. *International endodontic journal* 1991;**24**(1):24-6.
22. Koba K, Kimura Y, Matsumoto K, Watanabe H, Shinoki T, Kojy R, et al. Post-operative symptoms and healing after endodontic treatment of infected teeth using pulsed Nd:YAG laser. *Endodontics & dental traumatology* 1999;**15**(2):68-72.
23. Glennon JP, Ng YL, Setchell DJ, Gulabivala K. Prevalence of and factors affecting postpreparation pain in patients undergoing two-visit root canal treatment. *International endodontic journal* 2004;**37**(1):29-37.
24. Ng YL, Glennon JP, Setchell DJ, Gulabivala K. Prevalence of and factors affecting post-obturation pain in patients undergoing root canal treatment. *International endodontic journal* 2004;**37**(6):381-91.
25. Georgopoulou M, Anastassiadis P, Sykaras S. Pain after chemomechanical preparation. *International endodontic journal* 1986;**19**(6):309-14.
26. Jurcak JJ, Bellizzi R, Loushine RJ. Successful single-visit endodontics during Operation Desert Shield. *Journal of endodontics* 1993;**19**(8):412-3.
27. Imura N, Zuolo ML. Factors associated with endodontic flare-ups: a prospective study. *International endodontic journal* 1995;**28**(5):261-5.
28. Walton R, Fouad A. Endodontic interappointment flare-ups: a prospective study of incidence and related factors. *Journal of endodontics* 1992;**18**(4):172-7.
29. Alacam T. Incidence of postoperative pain following the use of different sealers in immediate root canal filling. *Journal of endodontics* 1985;**11**(3):135-7.
30. Torabinejad M, Cymerman JJ, Frankson M, Lemon RR, Maggio JD, Schilder H. Effectiveness of various medications on postoperative pain following complete instrumentation. *Journal of endodontics* 1994;**20**(7):345-54.
31. Sjogren U, Hagglund B, Sundqvist G, Wing K. Factors affecting the long-term results of endodontic treatment. *Journal of endodontics* 1990;**16**(10):498-504.
32. Siqueira JF, Jr., Rocas IN, Favieri A, Machado AG, Gahyva SM, Oliveira JC, et al. Incidence of postoperative pain after intracanal procedures based on an antimicrobial strategy. *Journal of endodontics* 2002;**28**(6):457-60.
33. Orstavik D. Time-course and risk analyses of the development and healing of chronic apical periodontitis in man. *International endodontic journal* 1996;**29**(3):150-5.
34. Pekruhn RB. The incidence of failure following single-visit endodontic therapy. *Journal of endodontics* 1986;**12**(2):68-72.
35. Kvist T, Molander A, Dahlen G, Reit C. Microbiological evaluation of one- and two-visit endodontic treatment of teeth with apical periodontitis: a randomized, clinical trial. *Journal of endodontics* 2004;**30**(8):572-6.
36. Rudner WL, Oliet S. Single-visit endodontics: a concept and a clinical study. *Compendium of continuing education in dentistry (Jamesburg, N.J. : 1995)* 1981;**2**(2):63-8.
37. Kenrick S. Endodontics: a multiple-visit or single-visit approach. *Australian endodontic journal : the journal of the Australian Society of Endodontology Inc* 2000;**26**(2):82-5.
38. Sjogren U, Figdor D, Persson S, Sundqvist G. Influence of infection at the time of root filling on the outcome of endodontic treatment of teeth with apical periodontitis. *International endodontic journal* 1997;**30**(5):297-306.

39. Maddox D, Walton R, Davis C. Incidence of posttreatment endodontic pain related to medication and other factors. *Journal of endodontics* 1977;**3**(12):447-52.
40. Fleming CH, Litaker MS, Alley LW, Eleazer PD. Comparison of classic endodontic techniques versus contemporary techniques on endodontic treatment success. *Journal of endodontics* 2010;**36**(3):414-8.
41. Singla R, Marwah N, Dutta S. Single Visit versus Multiple Visit Root Canal Therapy. *International journal of clinical pediatric dentistry* 2008;**1**(1):17-24.
42. Kalhoro FA, Mirza AJ. A study of flare-ups following single-visit root canal treatment in endodontic patients. *Journal of the College of Physicians and Surgeons--Pakistan : JCPSP* 2009;**19**(7):410-2.
43. Shaikh AG, Kalhoro FA, Dall AQ. Evaluation of post operative pain in single and multi visit endodontic therapy with rotary instruments. *Medical Forum Monthly* 2013;**24**(1):49-54.
44. Higgins JPT, Green S, editors. Cochrane Handbook for Systematic Reviews of Interventions. Version 5.10 (updated March 2011): The Cochrane Collaboration; 2011.
45. Akbar I, Iqbal A, Al-Omiri MK. Flare-up rate in molars with periapical radiolucency in one-visit vs two-visit endodontic treatment. *The journal of contemporary dental practice* 2013;**14**(3):414-8.
46. Albashaireh ZS, Alnegrish AS. Postobturation pain after single- and multiple-visit endodontic therapy. A prospective study. *Journal of dentistry* 1998;**26**(3):227-32.
47. Al-Negrish AR, Habahbeh R. Flare up rate related to root canal treatment of asymptomatic pulpally necrotic central incisor teeth in patients attending a military hospital. *Journal of dentistry* 2006;**34**(9):635-40.
48. DiRenzo A, Gresla T, Johnson BR, Rogers M, Tucker D, BeGole EA. Postoperative pain after 1- and 2-visit root canal therapy. *Oral surgery, oral medicine, oral pathology, oral radiology, and endodontics* 2002;**93**(5):605-10.
49. Dorasani G, Madhusudhana K, Chinni SK. Clinical and radiographic evaluation of single-visit and multi-visit endodontic treatment of teeth with periapical pathology: An in vivo study. *Journal of conservative dentistry : JCD* 2013;**16**(6):484-8.
50. Fava LR. A comparison of one versus two appointment endodontic therapy in teeth with non-vital pulps. *International endodontic journal* 1989;**22**(4):179-83.
51. Fava LR. A clinical evaluation of one and two-appointment root canal therapy using calcium hydroxide. *International endodontic journal* 1994;**27**(1):47-51.
52. Gesi A, Hakeberg M, Warfvinge J, Bergenholtz G. Incidence of periapical lesions and clinical symptoms after pulpectomy--a clinical and radiographic evaluation of 1- versus 2-session treatment. *Oral surgery, oral medicine, oral pathology, oral radiology, and endodontics* 2006;**101**(3):379-88.
53. Ghoddusi J, Javidi M, Zarrabi MH, Bagheri H. Flare-ups incidence and severity after using calcium hydroxide as intracanal dressing. *The New York state dental journal* 2006;**72**(4):24-8.
54. Ince B, Ercan E, Dalli M, Dulgergil CT, Zorba YO, Colak H. Incidence of postoperative pain after single- and multi-visit endodontic treatment in teeth with vital and non-vital pulp. *European journal of dentistry* 2009;**3**(4):273-9.
55. Jabeen S, Khurshiduzzaman M. Incidence of post obturation pain following single and multi visit root canal treatment in a teaching hospital of Bangladesh. *Mymensingh medical journal : MMJ* 2014;**23**(2):254-60.
56. Liu S, Leng Z-y. Short-term clinical effect of single-visit root-canal therapy in infected root canals. *Journal of Shanghai Jisobong University* 2013;**33**(7):1014-17.

57. Molander A, Warfvinge J, Reit C, Kvist T. Clinical and radiographic evaluation of one- and two-visit endodontic treatment of asymptomatic necrotic teeth with apical periodontitis: a randomized clinical trial. *Journal of endodontics* 2007;**33**(10):1145-8.
58. Mulhern JM, Patterson SS, Newton CW, Ringel AM. Incidence of postoperative pain after one-appointment endodontic treatment of asymptomatic pulpal necross in single-rooted teeth. *Journal of endodontics* 1982;**8**(8):370-5.
59. Oginni A, Udoye CI. Endodontic flare-ups: comparison of incidence between single and multiple visits procedures in patients attending a Nigerian teaching hospital. *Odonto-stomatologie tropicale = Tropical dental journal* 2004;**27**(108):23-7.
60. Paredes-Vieyra J, Enriquez FJ. Success rate of single- versus two-visit root canal treatment of teeth with apical periodontitis: a randomized controlled trial. *Journal of endodontics* 2012;**38**(9):1164-9.
61. Pekruhn RB. Single-visit endodontic therapy: a preliminary clinical study. *Journal of the American Dental Association (1939)* 1981;**103**(6):875-7.
62. Penesis VA, Fitzgerald PI, Fayad MI, Wenckus CS, BeGole EA, Johnson BR. Outcome of one-visit and two-visit endodontic treatment of necrotic teeth with apical periodontitis: a randomized controlled trial with one-year evaluation. *Journal of endodontics* 2008;**34**(3):251-7.
63. Peters LB, Wesselink PR. Periapical healing of endodontically treated teeth in one and two visits obturated in the presence or absence of detectable microorganisms. *International endodontic journal* 2002;**35**(8):660-7.
64. Prashanth MB, Tavane PN, Abraham S, Chacko L. Comparative evaluation of pain, tenderness and swelling followed by radiographic evaluation of periapical changes at various intervals of time following single and multiple visit endodontic therapy: an in vivo study. *The journal of contemporary dental practice* 2011;**12**(3):187-91.
65. Rao KN, Kandaswamy R, Umashetty G, Rathore VP, Hotkar C, Patil BS. Post-Obturation pain following one-visit and two-visit root canal treatment in necrotic anterior teeth. *Journal of international oral health : JIOH* 2014;**6**(2):28-32.
66. Risso PA, Cunha AJ, Araujo MC, Luiz RR. Postobturation pain and associated factors in adolescent patients undergoing one- and two-visit root canal treatment. *Journal of dentistry* 2008;**36**(11):928-34.
67. Singh S, Garg A. Incidence of post-operative pain after single visit and multiple visit root canal treatment: A randomized controlled trial. *Journal of conservative dentistry : JCD* 2012;**15**(4):323-7.
68. Trope M, Delano EO, Orstavik D. Endodontic treatment of teeth with apical periodontitis: single vs. multivisit treatment. *Journal of endodontics* 1999;**25**(5):345-50.
69. Waltimo T, Trope M, Haapasalo M, Orstavik D. Clinical efficacy of treatment procedures in endodontic infection control and one year follow-up of periapical healing. *Journal of endodontics* 2005;**31**(12):863-6.
70. Wang C, Xu P, Ren L, Dong G, Ye L. Comparison of post-obturation pain experience following one-visit and two-visit root canal treatment on teeth with vital pulps: a randomized controlled trial. *International endodontic journal* 2010;**43**(8):692-7.
71. Weiger R, Rosendahl R, Lost C. Influence of calcium hydroxide intracanal dressings on the prognosis of teeth with endodontically induced periapical lesions. *International endodontic journal* 2000;**33**(3):219-26.
72. Wong AW, Zhang S, Li SK, Zhu X, Zhang C, Chu CH. Incidence of post-obturation pain after single-visit versus multiple-visit non-surgical endodontic treatments. *BMC oral health* 2015;**15**:96.

73. Wong AW, Tsang CS, Zhang S, Li KY, Zhang C, Chu CH. Treatment outcomes of single-visit versus multiple-visit non-surgical endodontic therapy: a randomised clinical trial. *BMC oral health* 2015;**15**(1):162.
74. Yoldas O, Topuz A, Isci AS, Oztunc H. Postoperative pain after endodontic retreatment: single- versus two-visit treatment. *Oral surgery, oral medicine, oral pathology, oral radiology, and endodontics* 2004;**98**(4):483-7.

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	3
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	3
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	5-6
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	6
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	6
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	6-7
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	7
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Fig 1
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	Fig 1
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	8
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	8
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	9
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	9-10
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	9-10

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	9-10
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	9-10
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	Fig 1
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	Tab. 1
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	Tab. S2
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	Fig. 2-4
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	Fig. 2-4
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	Tab S2
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	Fig 2-4
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	13-15
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	15-16
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	16-17
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	17

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Single- or multiple visit root-canal treatment: Systematic Review, Meta-Analysis and Trial Sequential Analysis

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Single- or multiple visit root-canal treatment: Systematic Review, Meta-Analysis and Trial Sequential Analysis

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Keywords: Clinical outcomes; Clinical studies/trials; Comparative effectiveness research (CER); Endodontics; Evidence-based dentistry/health care; Systematic reviews and evidence-based medicine

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Single- or multiple visit root-canal treatment: Systematic Review, Meta-Analysis and Trial Sequential Analysis

Abstract

Objectives: Single-visit root-canal treatment has some advantages over conventional multi-visit treatment, but might increase the risk of complications. We systematically evaluated the risk of complications after single- or multiple visit root-canal treatment using meta- and trial-sequential analysis

Data: Controlled trials comparing single- versus multiple-visit root-canal treatment of permanent teeth were included. Trials needed to assess the risk of long-term complications (pain, infection, new/persisting/increasing peri-apical lesions ≥1 year after treatment), short-term pain, or flare-up (acute exacerbation of commencement or continuation of root-canal treatment).

Sources: Electronic databases (PubMed, Embase, Cochrane Central) were screened, random-effects meta-analyses performed, and trial-sequential analysis used to control for risk of random errors. Evidence was graded according to GRADE.

Study selection: 29 trials (4341 patients) were included, all but six showing high risk of bias. Based on ten trials (1257 teeth), risk of complications was not significantly different in single- versus multiple-visit treatment (RR: 1.00 [95% CI: 0.75/1.35]; weak evidence). Based on twenty studies (3008 teeth), risk of pain did not significantly differ between treatments (RR: 0.99 [95% CI: 0.76/1.30]; moderate evidence). Risk of flare-up was recorded by eight studies (1110 teeth) and was significantly higher after single- versus multiple-visit treatment (RR: 2.13 [95% CI: 1.16/3.89]; very weak evidence). Trial-sequential analysis revealed that firm evidence for benefit, harm or futility was not reached for any of the outcomes.

Conclusions: There is insufficient evidence to rule out whether important differences between both strategies exist.

Clinical significance: Dentists can provide root-canal treatment in one or multiple visits. Given the possibly increased risk of flare-ups, multiple-visit treatment might be preferred for certain teeth (e.g. those with peri-apical lesions).

Strength and limitations of this study

- This registered systematic review applies meta- and trial-sequential analysis to assess the strength and quantity of the accrued evidence towards different root-canal treatment strategies.
- The synthesized estimates are supported only by moderate or weak evidence according to GRADE.
- Firm evidence for benefit or harm of single- or multiple visit root-canal therapy as well as futility of further trials was not reached.

Introduction

After root-canal treatment, teeth can experience short- and/or long-term complications. Short-term complications include postoperative inflammation of peri-apical tissues leading to mild pain, or flare-up (i.e. an acute exacerbation of pulpal or peri-apical pathosis after root-canal treatment, like severe unbearable pain and swelling). Pain and swelling have been associated with instrumentation or irrigation transporting medications, infected debris and bacteria into the peri-apical tissues. Inadequate instrumentation and disinfection lead to bacterial persistence within the root-canals and consequent (re)contamination of peri-apical tissue.[1 2] Long-term outcomes include persisting inflammation and infection, resulting in abscess, sinus track formation, radiographic signs of peri-apical bone resorption or severe pain, with subsequent need to endodontically re-treat or remove teeth.[3 4] Both short and long-term outcomes seem to be affected by the preoperative condition of the tooth (tooth type, vitality, symptoms, peri-apical conditions).[4] Moreover, they might be affected by how root-canal treatments are provided.

Single-visit root-canal treatment attempts instrumentation, disinfection and obturation of the root-canal system in one visit. In contrast, multiple-visit root-canal treatment performs the instrumentation (or large parts of it) in the first and the obturation in the second visit, while the disinfection is provided in both visits via irrigation. Moreover, a disinfecting medication is placed in the canals between visits to allow further reduction of bacterial numbers. While single-visit treatment has obvious advantages over conventional multiple-visit treatment (like reduced number of visits, no need for repeated application of anesthetics or rubberdam, no intermediary restoration), it might be disadvantageous both with regards to short and long term outcomes.

A number of reviews have compared single- versus multiple visit root-canal treatment.[3 5-8] Some of these are outdated,[3 6] others investigate only short-term pain as outcome,[5] again others build on evidence beyond controlled trials like cohort studies or expert

opinions,[7] or pooled short- and long-term outcomes, which does not allow to weigh them against each other.[8] The present review aimed to comprehensively compare the currently available controlled trial data on short- and long-term complications of single- versus multiple visit root-canal treatment. Our primary objective was to answer the question: In patients needing root-canal treatment, is single-visit treatment significantly more effective than multiple visit treatment with regards to risk of long-term failure? The secondary objective was to compare both treatments with regards to risk of short-term postoperative pain as well as the risk of flare-up. We further investigated moderators of risks using subgroup or meta-regression analysis, and assessed how statistically robust current evidence is with regards to type I or II errors using trial sequential analysis. The review should guide the conduct of further studies and help to deduct clinical recommendations.

Methods

Eligibility criteria

This systematic review (registered at PROSPERO CRD42016036386) included trials that

- were randomized controlled trials or controlled trials without signs of selection bias (i.e. treatments were not allocated according to preoperative tooth status etc.). Sensitivity analyses were performed to account for the introduced risk of bias in case of treatment allocation not being at random.
- compared single-visit with multiple visit root-canal treatment in permanent teeth with closed apices and without internal resorption, regardless of the pre-operative condition (meta-regression and subgroup analyses were performed to account for different conditions).
- reported on risk of long-term complications (≥1 year after treatment), and/or risk of experiencing any short-term pain, and/or risk of short-term flare-up.

Outcomes

The primary outcome was the risk of long-term complications, defined as pain, infection/swelling/sinus track formation, or development, persistence or aggravation of peri-apical lesions or widening of the periodontal ligament etc. ≥1 year after treatment. No standard as to how peri-apical lesions needed to be assessed or categorized was set, as a range of classification systems are currently used.[3] Note that against our protocol, we did not assess the need of re-treatment due to long-term complications, as in most included trials it was not clearly stated, if re-treatments have been performed.

The secondary outcomes were

- risks of experiencing any short-term pain (<1 year after treatment) after obturation or after instrumentation or after both. For comparison of treatments, we considered only pain after obturation, not after instrumentation without obturation during multiple visit treatment. To detect the largest difference between treatments, incidence of pain was extracted at the shortest recording time point after treatment. As we did not separate mild, moderate or severe pain, and even included outcome measures like having taken any pain medication in this outcome, risk of any pain does not necessarily indicate a further treatment being required. Moreover, it should be noted that different degrees of pain where pooled. This was not avoidable given the different scales used, which cannot be synthesized otherwise., but introduces additional heterogeneity.
- risks of experiencing short-term flare-up, usually defined as an acute exacerbation of an asymptomatic pulpal and/or periradicular pathosis after the initiation or continuation of root canal treatment [9]. .Note that flare-up was not defined consistently across studies; some studies reported flare-up whilst having treated both symptomatic and asymptomatic teeth. We therefore defined flare-up as a short-term symptom (<1 year, usually directly after commencement or conclusion of root-canal treatment) which led or can be assumed to lead to a further intervention (like re-

accessing/re-instrumenting an incomplete treatment; completing an incision and drainage procedure, or re-performing root-canal treatment).

Searches

We searched Medline via PubMed, Embase via Ovid and Cochrane Central on March 10th 2016. Moreover, opengrey.eu was searched to identify accepted, but not published studies. There was no date restriction in our search. In addition, reference lists of identified full-texts were screened and cross-referenced. We contacted study authors if required to obtain full-texts. Neither authors nor journals were blinded to reviewers. No language restriction was set.

The applied search strategy can be found in Fig. 1.

Study records

Data management

A piloted spreadsheet was used for data extraction and management.

Selection process

Two reviewers (FS, GG) independently screened titles and then compared their findings. In case of disagreement, titles were included to obtain full texts. Full texts were assessed independently after de-duplication. Studies were included after agreement with consensus in cases of disagreement being reached through discussion.

Data collection process

Data extraction was performed independently by two reviewers (FS, GG). Disagreements were resolved through discussion.

Data items

The following items were collected: Author names, year, sample, setting, tooth type, pulp vitality, preoperative pain, presence of radiographically detectable periapical lesions,

instrumentation type, obturation type, irrigation, medication, intermediate restoration, no of visits, evaluation method, findings.

Outcomes

Outcomes and outcome measures were extracted. For studies reporting non-significant findings without any further information, this was extracted to allow including these into a sensitivity meta-analysis (see below).

Data synthesis

Meta-analysis

The statistical unit was the tooth. Clustering was near absent in most studies. Therefore, the risk of this approach leading to artificially narrow confidence intervals is low.[10] A continuity correction of +1 was performed in case of zero events. Random-effects meta-analysis using the DerSimonian-Laird estimator of variance was performed using Comprehensive Meta-Analysis 2.2.64 (Biostat, Englewood, NJ, USA), with Risk Ratios (RR) and 95% confidence intervals (95% CI) as effect estimates. Fixed effect models were used as well, but did not yield significantly different findings given the low level of heterogeneity. Unit-of analysis issues were handled as described in the appendix. Heterogeneity was assessed using Cochran's Q and I^2-statistics.[11] Funnel plot analysis and Egger test were performed to assess small study effects or publication bias.[12 13] RR were adjusted (RRa) to check the impact of possible publication bias.[14]

Subgroup and meta-regression analyses

Subgroup and meta-regression analyses were carried out to assess (1) the impact of a root-canal medication being used (or not) in multiple-visit treatment, (2) pulp vitality prior treatment, (3) preoperative pain, and (4) the presence of radiographically detectable peri-apical lesions on effect estimates. Details can be found in the appendix.

Confidence in data

Risk of bias was assessed and classified according to Cochrane guidelines.[13] Note that against our protocol, we did not assess performance bias (blinding of operators), as this is not feasible in trials comparing single- versus multiple-visit treatment.

In addition, trial sequential analysis (TSA) was performed to assess if quantitative findings are robust, and to calculate the required information size (RIS), i.e. the cumulative sample size needed to yield significant differences between treatments.[15 16] RIS is then adjusted for heterogeneity/diversity (DARIS). TSA additionally estimates trial sequential monitoring boundaries (TSMB), i.e. statistical thresholds for significance which are adapted depending on the so far reached sample size. Firm evidence is assumed to be reached when the Z-curve crosses the TSMB for benefit or harm before the DARIS was reached. Effect estimates supported by only few small trials are handled stricter than those supported by large samples. In addition to such superiority/inferiority TSMBs, monitoring boundaries for futility were calculated. These indicate if further trial conduct is likely to be futile, i.e. if sufficient evidence has been accrued to claim non-inferiority of treatments (which would be most relevant for this review). Further details have been reported elsewhere,[17] and can also be found in the appendix.

Evidence for each outcome effect estimate was graded according to the GRADE working group of evidence,[18] using Grade Profiler 3.6, and strength of recommendations deduced accordingly.[19]

Results

Results of the searches

From 817 records, 64 were screened full-text. After cross-referencing 67 articles were screened and 29 included (Tab. 1).[8 20-48] Excluded studies and reasons for exclusion can be found in the appendix (Tab. S1).

Overall, 4341 (mainly adult) patients had been treated (Tab. 1).

Table 1: Included studies.

Study	Patients	Vital/ pain/ lesion	Instr.	Medication	Obtur.	No. of visits	Pain Pain/sample single-visit; Pain/sample multiple-visit; recall	Flare-up Flare-ups/sample single-visit; Flare-ups/sample multiple-visit; recall	Long-term complications Complications/sample single-visit; Complications/sample multiple-visit; recall
Akbar 2013 [20]	100 adults or adolescents	no/ unclear/ yes	hand	calcium hydroxide	lateral	2		5/50; 4/50; 7 days	
Albashaireh & Alnegreshi 1998 [21]	300 adults or adolescents	yes/ no /unclear	hand	none	lateral	2	4/40; 3/36; 1 day		
		no/ no/ no	hand	none	lateral	2	33/102; 55/113; 1 day		
Al-Negrish & Habahbeh 2006 [22]	120 adults or adolescents	yes/ no/ no	hand	calcium hydroxide	lateral	2	8/54; 14/58; 2 days	1/54; 3/58; 7 days	
DiRenzo 2002 [23]	80 adults	both/ yes/ unclear	rotary	none	lateral	2	-/39; -/33; 1 day no significant difference on continuous scale		
Dorsani 2013 [24]	57 adults	no/ unclear/ yes	rotary	calcium hydroxide	lateral	2			10/24; 6/22; 1 year
Fava 1989 [25]	48 adults and children	no/ no/ unclear	hand	phenole	lateral	2	1/30; 0/30; 2 days		
Fava 1994 [26]	52 adults or adolescents	yes/ yes/ unclear	hand	calcium hydroxide	lateral	n.g.	2/30; 1/30; 1 day		
Gesi 2006 [28]	256 adults	yes/ both/ no	hand	calcium hydroxide	lateral	2	16/130; 18/126; 7 days		9/123; 8/121; 3 years
Ghoddusi 2006 [27]	60 adults	no/ both/ yes	hand	calcium hydroxide	lateral	2	1/20; 8/20; 3 days	7/20; 0/20; 3 days	
Ince 2009 [29]	306 adults	yes/ both/ no	hand	none	lateral	2	19/87; 16/66; 3 days		
		no/ both/ mixed	hand	none	lateral	2	9/66; 14/87; 3 days		
Jabeen 2014 [30]	120 adults or adolescents	no/ no/ no	unclear	calcium hydroxide	lateral	2	23/60; 11/60; 1day		
Liu & Leng 2013 [31]	143 adults	no/ unclear/ mixed	unclear	cortisomal	lateral	2-3	52/95; 28/48; 1 day		10/87; 4/42; 1 year
Molander 2007 [32]	94 adults	no/ no/ yes	rotary	calcium hydroxide	lateral	2			17/49; 10/40; 2 years
Mulhern 1982 [33]	60 adults or adolescents	no/ no/ mixed	hand	none	lateral	3	7/30; 6/30; 2 days		
Oginni 2004 [34]	255 adults	both/ both/ mixed	unclear	unclear	lateral	n.g.	58/107; 61/136; 1 day	19/104; 10/123; 7 days	
Paredes-Vieyra 2012 [35]	287 adults	no/ no/ yes	rotary	calcium hydroxide	lateral	2			5/146; 15/136; 2 years
Pekruhn 1981 [36]	102 cases of unclear age	unclear/ unclear/ unclear	hand	formocresol	vertical	2	8/51; 8/51; 1 day		
Penesis 2008 [37]	97 adults	no/ unclear/ yes	rotary	calcium hydroxide+ CHX	vertical	2			7/35; 7/31; 2 years
Peters and Wesslink 2002 [38]	39 adults	no/ no/ yes	hand	calcium hydroxide	lateral	2			0/21; 1/17; 4.5 years
Prashanth 2011 [39]	32 adults	no/ unclear/ yes	rotary	unclear	vertical	2	1/8; 0/8; 2 days		
		yes/ unclear/ no	rotary	unclear	vertical	2	1/8; 1/8; 2 days		
Rao 2014	148 adults	no/	rotary	none	lateral	2	-/74; -/74 1 day		

[40]		unclear/ unclear					no significant difference on continuous scale		
Risso 2008 [41]	118 adolescents	no/ both/ mixed	hand	calcium hydroxide	lateral	2	-/57;-/61;1 day results not reported	1/57;1/61; 10 days	
Singh and Kargh 2012 [42]	200 adults	both/ unclear/ no	rotary	none	lateral	2	-/94; -/94; 1 day no significant difference on continuous scale	0/9; 0/94; 6 days	
Trope 1999 [44], Waltimo 2005 [43]	81 adults	no/ unclear/ yes	hand	calcium hydroxide	lateral	2			9/45; 6/31; 1 year
Wang 2010 [45]	100 adults	yes/ yes/ no	rotary	calcium hydroxide	lateral	2	28/43; 27/46; 1 day	1/43; 1/46; 7 days	
Weiger 2000 [46]	73 adults or adolescents	no/ both/ yes	hand	calcium hydroxide	lateral	n.g.			3/36; 2/31; up to 5 years
Wong 2015a [47]	567 adults	both/ both/ mixed	rotary	calcium hydroxide	lateral or core carrier	2	68/275; 88/263; 1 day		
Wong 2015b [8]	228 adults	both/ both/ mixed	rotary	calcium hydroxide	core carrier	2-3	25/117; 12/103; 7 days		13/117; 13/103; 2 years
Yoldas 2004 [48]	218 adults	no/ both/ re-treatment	both	calcium hydroxide + CHX	lateral	2	44/106; 32/112; 7 days	8/106; 2/112; 7 days	

Abbreviations: CHX chlorhexidine, n.g. not given, obtur. obturation

Six trials treated only teeth with vital pulps, six treated vital and non-vital teeth or did not specify vitality; the remaining trials treated non-vital teeth. Three trials clearly stated to treat only teeth with preoperative pain, 15 treated both painful and painless teeth or did not state any details on preoperative symptoms, the remaining trials treated only teeth without preoperative symptoms. Ten trials included only teeth with peri-apical lesions, 13 trials did not report on radiographic status of the peri-apex or treated both teeth with and without lesions; the remaining trials treated only teeth without any detectable lesions.

Six trials were found to have low risk of bias (Tab. S2), the remaining trials showed high or unclear overall risk of bias. This was mainly due to a lack of examiner blinding or allocation concealment. Two trials did not at all report on randomization, and were treated accordingly in the performed meta-analysis. The majority of trials mentioned randomization, but did not state how sequences were generated. Attrition was generally limited (as most trials did only assess short-term pain, see below), as was risk of selective reporting.

Risk of long-term complications

Long-term complications were investigated by ten trials, with a total of 1257 teeth being treated. Mean follow-up was 2.3 years (range: 1-5 years). All trials had used calcium hydroxide as medication in the multiple-visit group. All but two trials had high risk of bias. Risk of complications was not significantly different in single- versus multiple-visit treatment (RR: 1.00 [95% CI: 0.75/1.35]). Heterogeneity was low. Publication bias was not detected via Egger's test (p=0.36) or funnel plot analysis (Fig. 2a, Appendix Fig. S1a).

Preoperative conditions were not found to significantly impact on effect estimates (Tab. 2).

Table 2: Meta-regression analysis. LogRR and 95% CI are given to allow comparing relative effect estimates between subgroups of treatments. n: number of studies; n/a not available (as all studies used calcium hydroxide).

	Outcomes		
Subgroups	**Long-term complications (n=10)**	**Any postoperative pain (n=23)**	**Postoperative flare-up (n=8)**
Pain-free versus painful teeth	-0.33 (-1.47/1.14)	0.15 (-0.50/0.80)	1.10 (-2.44/4.63)
Vital versus non-vital teeth	0.10 (-0.90/1.10)	-0.02 (-0.60/0.58)	-0.08 (-2.26/2.10)
Teeth with peri-apical lesions versus teeth without lesions	-0.13 (-1.22/0.98)	-1.18 (-2.91/0.55)	0.79 (-0.87/2.46)
Calcium hydroxide medication versus no medication	n/a	0.11 (-0.27/0.50)	-0.27 (-1.29/0.74)

Studies which did not state to have randomly allocated treatments did not find significantly different risk ratios (p=0.35). Using TSA, we found neither the conventional thresholds for benefit or harm nor the TSMB for benefit, harm or futility to be reached. Sample size was far below DARIS (Fig. 2b). Given that risk of bias was serious and the number of events low (leading to imprecision), our confidence in this finding was weak.

Risk of experiencing any postoperative pain

20 studies used binary estimates to express risk of short-term pain. Of these, three had used a factorial design, with resulting subgroups being handled as independent studies. Three further studies used visual-analogue scales and reported pain to not be significantly different; these were included in a sensitivity analyses. For the base-case analysis, a total of 3008 teeth were available and assessed. Pain had been recorded after a mean of 2 days (range: 1-7 days) postoperatively. Three trials had compared pain only after instrumentation, the other studies compared pain after obturation. All but three trials showed high risk of bias.

Risk of pain was not significantly different in single- versus multiple-visit treatment (RR: 0.99 [95% CI: 0.76/1.30]). Heterogeneity was moderate. There was no indication for publication bias via Egger's test (p=0.46) or funnel plot analysis (Fig. 3a, Appendix Fig. S1b). Preoperative conditions or the use of a calcium hydroxide instead of no root-canal medication between visits had no significant impact on effect estimates (Tab. 2). Studies which did not state to have randomly allocated treatments did not find significantly different risk ratios compared with studies which had clearly stated randomization (p=0.46). Including imputed studies which had only reported that differences between groups were non-significant (but had not given an effect estimate) increased the total number of assessed teeth to 3417, but did not significantly change our estimates (RR=1.00 [0.86/1.21]). Excluding those trials which only reported on pain after instrumentation, not obturation, also had no significant impact (RR=0.99 [0.84/1.17]). Using TSA, we found the conventional thresholds for benefit to be spuriously crossed, while the TSMB for benefit was not reached. Futility boundaries were not constructible due to too few data being available. The sample size was far below DARIS (Fig. 3b). Given the serious risk of bias, but only limited evidence for imprecision, this finding is supported by moderate evidence according to GRADE.

Risk of flare-up

Risk of flare-up was recorded by eight studies. A total of 1110 teeth had been followed over a period of 7-10 days. All studies stated to be randomized trials, two studies showed low, the rest high risk of bias.

Risk of flare-up was significantly higher after single- versus multiple-visit treatment (RR: 2.13 [95% CI: 1.16/3.89]). Heterogeneity was low. There was some indication for publication bias based on funnel plot analysis, but not Egger's test (p=0.26). Adjusting the estimate accordingly increased the RR (Fig. 4a, Appendix Fig. S1c). Preoperative conditions and the root-canal medication had no significant impact on effect estimates (Tab. 2). Using TSA, we found the conventional thresholds for harm to be spuriously crossed, while the TSMB for harm was not reached. Futility boundaries were not constructible due to too few data being available. The sample size was far below DARIS (Fig. 4b). Given the serious risk of bias, imprecision and publication bias being present, our confidence in this finding is supported by only very weak evidence according to GRADE.

Discussion

Even after optimal root-canal disinfection via instrumentation and irrigation, bacteria usually remain within the root-canal system.[49 50] During multiple-visit root-canal treatment, an antibacterial medication like calcium hydroxide is placed in the root-canals, thereby aiming to further disinfect the canals between treatment appointments, the efficacy of which remains unclear at present.[49 51-53] In contrast, in single-visit root-canal treatment any further appointments and intra-canal medications are omitted, and the root-canal system obturated directly after instrumentation and irrigation, aiming to seal remaining bacteria and deprive them from both space and nutrition.[3 46 54 55]

For risk of long-term complications, we did not find a difference between single and multiple visit endodontic treatment. This was our primary outcome, as such complications oftentimes decide the fate of the tooth.[56-58] It is noteworthy that this was supported by a range of studies (i.e. studies with high or low risk, small or large samples, in adults or adolescents, vital or non-vital teeth, teeth with or without peri-apical lesions) with relatively homogenous findings. Only one trial found significant differences between groups (favoring single-visit treatment),[35] all others did not find one treatment significantly superior over the other.

Based on our analyses, the discussed confounders do not seem to significantly affect the relative risk of complications. Even in teeth with peri-apical lesions, single-visit treatment showed no significantly different risk of complications. This finding is in line with that from a previous review.[6] We want to highlight that our performed meta-regression and subgroup analyses are potentially underpowered, with high risk of type II errors. In general, our findings on the risk of complications outcome are supported by limited data, as indicated by TSA. Based on this analysis, no firm evidence on benefit, harm or futility is available (while the cumulative Z-curve never crossed any threshold for significance, once more confirming a trend towards non-difference of treatments).

The resulting evidence was graded as weak, mainly due to risk of bias of trials. Thus, a number of recommendations towards future studies need to be made: First, future trials should have higher internal validity, e.g. by performing and reporting on sequence generation, by sufficiently concealing the allocation, and by blinding assessors, all to reduce the risk of selection and detection bias. We are well aware that blinding operators or patients is impossible in such trials; future reviews should reflect on this when assessing risk of bias (as we did accordingly). Second, trials should be performed in realistic (primary care) settings with sufficiently long follow-up periods, as complications are expected to occur long-term. Third, trials should aim to investigate the relevance of preoperative conditions as possible confounders, as current data are insufficient to conclude on the suitability of single- versus multiple-visit treatment in different teeth or patients.

We also found single-visit treatment to not significantly increase the risk of short-term postoperative pain, which is in line with findings from previous reviews.[3 6 59] Pain is a relevant outcome, despite being reported only for brief periods after treatment and not being a strong predictor for success,[50] as it is directly burdening patients and could influence their attitude and behavior towards future endodontic treatment. Our findings were again relatively consistent between trials regardless of their risk of bias, setting, patients or treated teeth. Only three studies found significant differences between groups; two in favor of single-

visit treatment,[21 27] one in favor of multiple-visit treatment.[30] All three were performed in non-vital teeth. It is again important to note that while we did not identify significant confounders (which is in line with previous findings),[60] our meta-regression analyses are (as discussed) of limited power. However, the overall number of treated teeth was relatively high, and while current data was insufficient to establish firm evidence, we expect futility boundaries of TSA to be reached if future trials confirm these findings. Given the discussed uncertainties associated with the preoperative condition (vitality, symptoms), researchers should account for these confounders when designing and evaluating future trials in the field.

We found single-visit treatment to significantly increase the risk of flare-up, which is in agreement with a previously identified increased risk of swelling after single-visit treatment.[3] It should be highlighted that our analysis for this outcome was built on only few, mainly high risk trials, and that one particular study contributed a lot to the effect estimate given its weighting.[34] This weighting was the result of the high incidence of flare-up in this study (20% in the single-visit group), which is much higher than that in all other trials. Excluding this study from the analysis decreased the effect estimates, with no significant difference between groups remaining (RR: 1.85 [0.89/3.86]). Given that TSA indicated that no firm evidence has been reached so far, caution is thus required when interpreting our finding regarding flare-up. Such caution is further justified as flare-ups occurring directly after treatment as well as up to 7 days after instrumentation (or obturation) were pooled. Moreover, risk of flare-ups might be affected by further factors like patients' age, gender or systemic conditions. While patients with systemic conditions were excluded in all studies, insufficient information was available regarding gender and age distribution. Future studies should report in more detail on these aspects.

This review has a number of limitations. First, it builds only on randomized or at least controlled trials. While we see the value of practice-based long-term cohort studies (which have higher external validity and yield findings in a more relevant timeframe), we actively

restricted our review on controlled studies to minimize the risk of selection bias, the impact of which can be expected to be potentially severe given that treatment decisions might be made based on the preoperative condition of the tooth. For example, dentists might be more willing to perform single-visit treatment in vital teeth, or molars might be treated in multiple visits more often due to practical reasons. This would greatly distort the true relative efficacy of both therapies.

Second, our primary outcome, complications, is a composite of different components like long-term pain, clinical signs of inflammation and infection (swelling, sinus track formation), and radiographic success (which does not need the patient to experience symptoms). For each component, a decision to re-treat or not might differ depending on who is deciding: Dentists (and researchers specializing in endodontics) might see a persistent peri-apical lesion as an indication to re-treat even in the absence of symptoms (anticipating such symptoms to occur at some stage in the future, with poorer prognosis for re-treatments). In contrast, patients might not be willing to re-treat such tooth (which might as well be justified when considering the success rates of the available re-treatments and the resulting treatment costs).[58]

Third, one of our secondary outcomes, the risk of experiencing any postoperative pain, does not account for the degree of pain, losing a significant amount of information. That was done as most trials reported pain using either a binary scales (pain yes/no) or ordinal scales, which did not always use identical categories and pose great difficulties when pooling them (or require the definition of a certain pain threshold, which is usually arbitrary). Future studies should use continuous outcome measures like visual analogues scales, allowing to fully display the recorded information on pain. It is noteworthy that those studies which used such scales also found no significant difference of pain levels between treatments.

Last, most included trials reported only on very limited periods after treatment. While this might be acceptable for short-term pain, a follow-up of mean 2.3 years is insufficient to truly

reflect “long-term” complications (as is applied definition of minimum one year follow-up to consider a complication as long-term). This is closely related with the discussed limitations of randomized trials, which are seldom able to follow-up teeth for much longer given the high associated efforts and costs.

Future trials are thus needed to gain firm evidence whether differences in outcomes between single or multiple visit root-canal treatment exist. To improve validity and comparability, these trials should aim for standardized outcome measures (e.g. visual analogue scale for pain assessment; agreed definition for success/failure), long-term follow-up periods and limited risk of bias (while certain bias cannot be fully excluded). They should best be performed in representative settings and populations and report in detail on confounders of treatment success.

In conclusion and within the limitations of this review, there is insufficient evidence to rule out whether important differences in outcomes between one or multiple visit root-canal treatment exist.. Given the possibly increased risk of flare-up, a careful recommendation could be to prefer multiple-visit treatment in teeth where the risk if complication is increased (e.g. teeth with existing peri-apical lesions).

Figure Legends

Figure 1: Study flow. Database screening was performed using a four-pronged search strategy, combining four domains of the search using Boolean operators. Number of studies yielded in Medline by each search domain are shown in the upper boxes; combining these boxes led to the number of results as shown for each database.

Figure 2: Risk of long-term complications after single- versus multiple-visit root-canal treatment. (a) Forest plot, with Risk Ratio (RR) and 95% confidence intervals (CI) per study and overall (black diamond) being given. Heterogeneity across studies is indicated by I^2 and Q. Low risk of bias and lack of random allocation of treatment is indicated by asterisks and hashtag. (b) Trial sequential analysis. The cumulative Z-score (black), i.e., the accumulated level of significance, was plotted against the number of participants (N) accrued, which was compared with the diversity-adjusted required information size (DARIS). The Z-curve does not cross the conventional thresholds for superiority or inferiority (hatched grey lines). Neither the DARIS nor TSMB (grey solid lines) were reached. The information fraction was too small to draw trial sequential futility boundaries.

Figure 3: Risk of experiencing any postoperative pain after single- versus multiple-visit root-canal treatment. (a) Forest plot. Low risk of bias and lack of random allocation of treatment is indicated by asterisks and hashtag. Studies which compared treatments in different subgroup of teeth were handled as independent studies and are indicated accordingly. (b) Trial sequential analysis. The information fraction was too small to draw trial sequential futility boundaries.

Figure 4: Risk of experiencing flare-up after single- versus multiple-visit root-canal treatment. (a) Forest plot. RR and 95% CI were adjusted for publication bias using trim-and-fill (RRa). Low risk of bias and lack of random allocation of treatment is indicated by asterisks and hashtag. Studies which compared treatments in different subgroup of teeth were handled as independent studies and are indicated accordingly. (b) Trial sequential analysis. The information fraction was too small to draw trial sequential futility boundaries.

Contributorship statement

F. Schwendicke, contributed to conception, design, data acquisition, analysis, and interpretation, drafted and critically revised the manuscript; G. Göstemeyer, contributed to conception, design, data acquisition, interpretation and critically revised the manuscript.

Competing interests

None declared.

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Data sharing statement

No additional data are available.

References

1. Glennon JP, Ng YL, Setchell DJ, et al. Prevalence of and factors affecting postpreparation pain in patients undergoing two-visit root canal treatment. International endodontic journal 2004;**37**(1):29-37
2. Ng YL, Glennon JP, Setchell DJ, et al. Prevalence of and factors affecting post-obturation pain in patients undergoing root canal treatment. International endodontic journal 2004;**37**(6):381-91 doi: 10.1111/j.1365-2591.2004.00820.x[published Online First: Epub Date]|.
3. Figini L, Lodi G, Gorni F, et al. Single versus multiple visits for endodontic treatment of permanent teeth. The Cochrane database of systematic reviews 2007(4):Cd005296 doi: 10.1002/14651858.CD005296.pub2[published Online First: Epub Date]|.
4. Ng YL, Mann V, Rahbaran S, et al. Outcome of primary root canal treatment: systematic review of the literature – Part 2. Influence of clinical factors. International endodontic journal 2008;**41**(1):6-31 doi: 10.1111/j.1365-2591.2007.01323.x[published Online First: Epub Date]|.
5. Raju TB, Seshadri A, Vamsipavani B, et al. Evaluation of pain in single and multi rooted teeth treated in single visit endodontic therapy. Journal of international oral health : JIOH 2014;**6**(1):27-32
6. Su Y, Wang C, Ye L. Healing rate and post-obturation pain of single- versus multiple-visit endodontic treatment for infected root canals: a systematic review. Journal of endodontics 2011;**37**(2):125-32 doi: 10.1016/j.joen.2010.09.005[published Online First: Epub Date]|.
7. De-Deus G, Canabarro A. Strength of recommendation for single-visit root canal treatment: grading the body of the evidence using a patient-centered approach. International endodontic journal 2016 doi: 10.1111/iej.12621[published Online First: Epub Date]|.
8. Wong AW, Tsang CS, Zhang S, et al. Treatment outcomes of single-visit versus multiple-visit non-surgical endodontic therapy: a randomised clinical trial. BMC oral health 2015;**15**(1):162 doi: 10.1186/s12903-015-0148-x[published Online First: Epub Date]|.
9. American Association of Endodontists. Glossary of endodontic terms. 7th edition. Secondary Glossary of endodontic terms. 7th edition. 2003.
10. Masood M, Masood Y, Newton JT. The clustering effects of surfaces within the tooth and teeth within individuals. Journal of dental research 2015;**94**(2):281-8 doi: 10.1177/0022034514559408[published Online First: Epub Date]|.
11. Higgins JPT, Thompson SG. Quantifying heterogeneity in a meta-analysis. Statistics in medicine 2002;**21**(11):1539-58 doi: 10.1002/sim.1186[published Online First: Epub Date]|.
12. Egger M, Smith GD, Schneider M, et al. Bias in meta-analysis detected by a simple, graphical test. BMJ 1997;**315**(7109):629-34 doi: 10.1136/bmj.315.7109.629[published Online First: Epub Date]|.

13. Higgins JPT, Green S, editors. *Cochrane Handbook for Systematic Reviews of Interventions*. Version 5.10 (updated March 2011): The Cochrane Collaboration, 2011.
14. Duval S, Tweedie R. Trim and fill: A simple funnel-plot-based method of testing and adjusting for publication bias in meta-analysis. Biometrics 2000;**56**(2):455-63
15. Wetterslev J, Thorlund K, Brok J, et al. Trial sequential analysis may establish when firm evidence is reached in cumulative meta-analysis. J Clin Epidemiol 2008;**61**(1):64-75 doi: 10.1016/j.jclinepi.2007.03.013[published Online First: Epub Date]|.
16. Thorlund K, Engstrøm J, Wetterslev J, et al. User Manual for Trial Sequential Analysis (TSA). http://www.ctu.dk/tsa/files/tsa_manual.pdf 2011:1-115
17. Schwendicke F, Goestemeyer G, Gluud C. Cavity lining after excavating caries lesions: meta-analysis and trial sequential analysis of randomized clinical trials. Journal of Dentistry 2015;**doi: 10.1016/j.jdent.2015.07.017**
18. Atkins D, Best D, Briss PA, et al. Grading quality of evidence and strength of recommendations. BMJ 2004;**328**(7454):1490
19. Andrews J, Guyatt G, Oxman AD, et al. GRADE guidelines: 14. Going from evidence to recommendations: the significance and presentation of recommendations. J Clin Epidemiol 2013;**66**(7):719-25 doi: 10.1016/j.jclinepi.2012.03.013[published Online First: Epub Date]|.
20. Akbar I, Iqbal A, Al-Omiri MK. Flare-up rate in molars with periapical radiolucency in one-visit vs two-visit endodontic treatment. The journal of contemporary dental practice 2013;**14**(3):414-8
21. Albashaireh ZS, Alnegrish AS. Postobturation pain after single- and multiple-visit endodontic therapy. A prospective study. Journal of dentistry 1998;**26**(3):227-32
22. Al-Negrish AR, Habahbeh R. Flare up rate related to root canal treatment of asymptomatic pulpally necrotic central incisor teeth in patients attending a military hospital. Journal of dentistry 2006;**34**(9):635-40 doi: 10.1016/j.jdent.2005.12.007[published Online First: Epub Date]|.
23. DiRenzo A, Gresla T, Johnson BR, et al. Postoperative pain after 1- and 2-visit root canal therapy. Oral surgery, oral medicine, oral pathology, oral radiology, and endodontics 2002;**93**(5):605-10
24. Dorasani G, Madhusudhana K, Chinni SK. Clinical and radiographic evaluation of single-visit and multi-visit endodontic treatment of teeth with periapical pathology: An in vivo study. Journal of conservative dentistry : JCD 2013;**16**(6):484-8 doi: 10.4103/0972-0707.120933[published Online First: Epub Date]|.
25. Fava LR. A comparison of one versus two appointment endodontic therapy in teeth with non-vital pulps. International endodontic journal 1989;**22**(4):179-83
26. Fava LR. A clinical evaluation of one and two-appointment root canal therapy using calcium hydroxide. International endodontic journal 1994;**27**(1):47-51
27. Ghoddusi J, Javidi M, Zarrabi MH, et al. Flare-ups incidence and severity after using calcium hydroxide as intracanal dressing. The New York state dental journal 2006;**72**(4):24-8
28. Gesi A, Hakeberg M, Warfvinge J, et al. Incidence of periapical lesions and clinical symptoms after pulpectomy--a clinical and radiographic evaluation of 1- versus 2-session treatment. Oral surgery, oral medicine, oral pathology, oral radiology, and endodontics 2006;**101**(3):379-88 doi: 10.1016/j.tripleo.2005.05.073[published Online First: Epub Date]|.

29. Ince B, Ercan E, Dalli M, et al. Incidence of postoperative pain after single- and multi-visit endodontic treatment in teeth with vital and non-vital pulp. European journal of dentistry 2009;**3**(4):273-9
30. Jabeen S, Khurshiduzzaman M. Incidence of post obturation pain following single and multi visit root canal treatment in a teaching hospital of Bangladesh. Mymensingh medical journal : MMJ 2014;**23**(2):254-60
31. Liu S, Leng Z-y. Short-term clinical effect of single-visit root-canal therapy in infected root canals. Journal of Shanghai Jisobong University 2013;**33**(7):1014-17
32. Molander A, Warfvinge J, Reit C, et al. Clinical and radiographic evaluation of one- and two-visit endodontic treatment of asymptomatic necrotic teeth with apical periodontitis: a randomized clinical trial. Journal of endodontics 2007;**33**(10):1145-8 doi: 10.1016/j.joen.2007.07.005[published Online First: Epub Date]|.
33. Mulhern JM, Patterson SS, Newton CW, et al. Incidence of postoperative pain after one-appointment endodontic treatment of asymptomatic pulpal necross in single-rooted teeth. Journal of endodontics 1982;**8**(8):370-5
34. Oginni A, Udoye CI. Endodontic flare-ups: comparison of incidence between single and multiple visits procedures in patients attending a Nigerian teaching hospital. Odonto-stomatologie tropicale = Tropical dental journal 2004;**27**(108):23-7
35. Paredes-Vieyra J, Enriquez FJ. Success rate of single- versus two-visit root canal treatment of teeth with apical periodontitis: a randomized controlled trial. Journal of endodontics 2012;**38**(9):1164-9 doi: 10.1016/j.joen.2012.05.021[published Online First: Epub Date]|.
36. Pekruhn RB. Single-visit endodontic therapy: a preliminary clinical study. Journal of the American Dental Association (1939) 1981;**103**(6):875-7
37. Penesis VA, Fitzgerald PI, Fayad MI, et al. Outcome of one-visit and two-visit endodontic treatment of necrotic teeth with apical periodontitis: a randomized controlled trial with one-year evaluation. Journal of endodontics 2008;**34**(3):251-7 doi: 10.1016/j.joen.2007.12.015[published Online First: Epub Date]|.
38. Peters LB, Wesselink PR. Periapical healing of endodontically treated teeth in one and two visits obturated in the presence or absence of detectable microorganisms. International endodontic journal 2002;**35**(8):660-7
39. Prashanth MB, Tavane PN, Abraham S, et al. Comparative evaluation of pain, tenderness and swelling followed by radiographic evaluation of periapical changes at various intervals of time following single and multiple visit endodontic therapy: an in vivo study. The journal of contemporary dental practice 2011;**12**(3):187-91
40. Rao KN, Kandaswamy R, Umashetty G, et al. Post-Obturation pain following one-visit and two-visit root canal treatment in necrotic anterior teeth. Journal of international oral health : JIOH 2014;**6**(2):28-32
41. Risso PA, Cunha AJ, Araujo MC, et al. Postobturation pain and associated factors in adolescent patients undergoing one- and two-visit root canal treatment. Journal of dentistry 2008;**36**(11):928-34 doi: 10.1016/j.jdent.2008.07.006[published Online First: Epub Date]|.
42. Singh S, Garg A. Incidence of post-operative pain after single visit and multiple visit root canal treatment: A randomized controlled trial. Journal of conservative dentistry : JCD 2012;**15**(4):323-7 doi: 10.4103/0972-0707.101888[published Online First: Epub Date]|.

43. Waltimo T, Trope M, Haapasalo M, et al. Clinical efficacy of treatment procedures in endodontic infection control and one year follow-up of periapical healing. Journal of endodontics 2005;**31**(12):863-6
44. Trope M, Delano EO, Orstavik D. Endodontic treatment of teeth with apical periodontitis: single vs. multivisit treatment. Journal of endodontics 1999;**25**(5):345-50 doi: 10.1016/s0099-2399(06)81169-6[published Online First: Epub Date]|.
45. Wang C, Xu P, Ren L, et al. Comparison of post-obturation pain experience following one-visit and two-visit root canal treatment on teeth with vital pulps: a randomized controlled trial. International endodontic journal 2010;**43**(8):692-7 doi: 10.1111/j.1365-2591.2010.01748.x[published Online First: Epub Date]|.
46. Weiger R, Rosendahl R, Lost C. Influence of calcium hydroxide intracanal dressings on the prognosis of teeth with endodontically induced periapical lesions. International endodontic journal 2000;**33**(3):219-26
47. Wong AW, Zhang S, Li SK, et al. Incidence of post-obturation pain after single-visit versus multiple-visit non-surgical endodontic treatments. BMC oral health 2015;**15**:96 doi: 10.1186/s12903-015-0082-y[published Online First: Epub Date]|.
48. Yoldas O, Topuz A, Isci AS, et al. Postoperative pain after endodontic retreatment: single- versus two-visit treatment. Oral surgery, oral medicine, oral pathology, oral radiology, and endodontics 2004;**98**(4):483-7 doi: 10.1016/s1079210404002161[published Online First: Epub Date]|.
49. Bystrom A, Sundqvist G. Bacteriologic evaluation of the efficacy of mechanical root canal instrumentation in endodontic therapy. Scandinavian journal of dental research 1981;**89**(4):321-8
50. Sjogren U, Figdor D, Persson S, et al. Influence of infection at the time of root filling on the outcome of endodontic treatment of teeth with apical periodontitis. International endodontic journal 1997;**30**(5):297-306
51. Han GY, Park SH, Yoon TC. Antimicrobial activity of Ca(OH)2 containing pastes with Enterococcus faecalis in vitro. Journal of endodontics 2001;**27**(5):328-32 doi: 10.1097/00004770-200105000-00004[published Online First: Epub Date]|.
52. Siqueira JF, Jr., Lopes HP, de Uzeda M. Recontamination of coronally unsealed root canals medicated with camphorated paramonochlorophenol or calcium hydroxide pastes after saliva challenge. Journal of endodontics 1998;**24**(1):11-4 doi: 10.1016/s0099-2399(98)80204-5[published Online First: Epub Date]|.
53. DiFiore PM, Peters DD, Setterstrom JA, et al. The antibacterial effects of calcium hydroxide apexification pastes on Streptococcus sanguis. Oral surgery, oral medicine, and oral pathology 1983;**55**(1):91-4
54. Soltanoff W. A comparative study of the single-visit and the multiple-visit edodontic procedure. Journal of endodontics 1978;**4**(9):278-81
55. Oliet S. Single-visit endodontics: a clinical study. Journal of endodontics 1983;**9**(4):147-52 doi: 10.1016/s0099-2399(83)80036-3[published Online First: Epub Date]|.
56. Ng YL, Mann V, Gulabivala K. Outcome of secondary root canal treatment: a systematic review of the literature. International endodontic journal 2008;**41**(12):1026-46 doi: 10.1111/j.1365-2591.2008.01484.x[published Online First: Epub Date]|.
57. Del Fabbro M, Taschieri S, Testori T, et al. Surgical versus non-surgical endodontic re-treatment for periradicular lesions. The Cochrane database of systematic reviews 2007(3):Cd005511 doi: 10.1002/14651858.CD005511.pub2[published Online First: Epub Date]|.

58. Schwendicke F, Stolpe M. Secondary Treatment for Asymptomatic Root Canal Treated Teeth: A Cost-effectiveness Analysis. Journal of endodontics 2015;**41**(6):812-6 doi: 10.1016/j.joen.2015.01.013[published Online First: Epub Date]|.
59. Wong AW, Zhang C, Chu CH. A systematic review of nonsurgical single-visit versus multiple-visit endodontic treatment. Clinical, cosmetic and investigational dentistry 2014;**6**:45-56 doi: 10.2147/ccide.s61487[published Online First: Epub Date]|.
60. Sathorn C, Parashos P, Messer H. The prevalence of postoperative pain and flare-up in single- and multiple-visit endodontic treatment: a systematic review. International endodontic journal 2008;**41**(2):91-9 doi: 10.1111/j.1365-2591.2007.01316.x[published Online First: Epub Date]|.

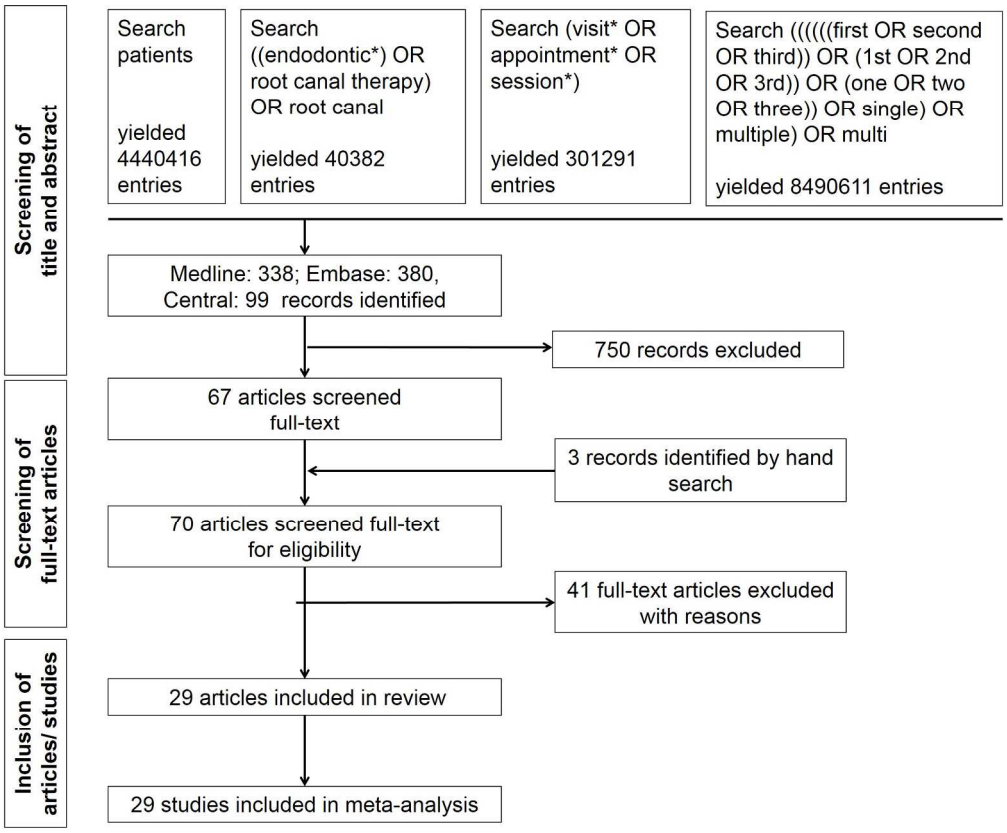

Figure 1: Study flow. Database screening was performed using a four-pronged search strategy, combining four domains of the search using Boolean operators. Number of studies yielded in Medline by each search domain are shown in the upper boxes; combining these boxes led to the number of results as shown for each database.

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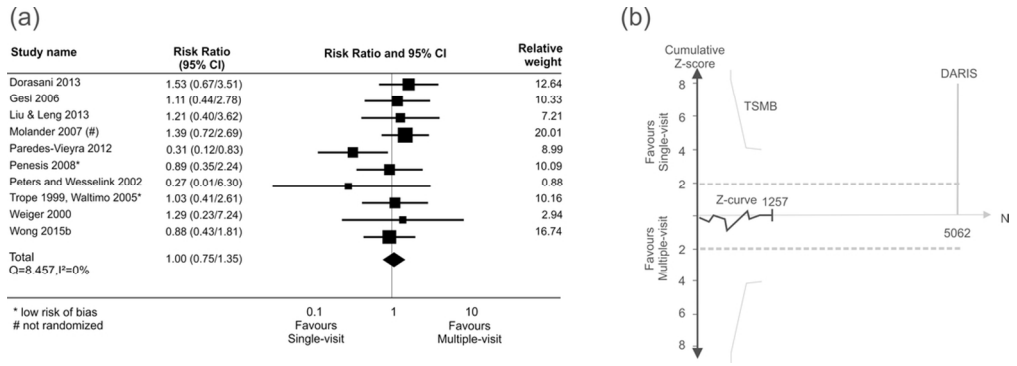

Figure 2: Risk of long-term complications after single- versus multiple-visit root-canal treatment. (a) Forest plot, with Risk Ratio (RR) and 95% confidence intervals (CI) per study and overall (black diamond) being given. Heterogeneity across studies is indicated by I^2 and Q. Low risk of bias and lack of random allocation of treatment is indicated by asterisks and hashtag. (b) Trial sequential analysis. The cumulative Z-score (black), i.e., the accumulated level of significance, was plotted against the number of participants (N) accrued, which was compared with the diversity-adjusted required information size (DARIS). The Z-curve does not cross the conventional thresholds for superiority or inferiority (hatched grey lines). Neither the DARIS nor TSMB (grey solid lines) were reached. The information fraction was too small to draw trial sequential futility boundaries.

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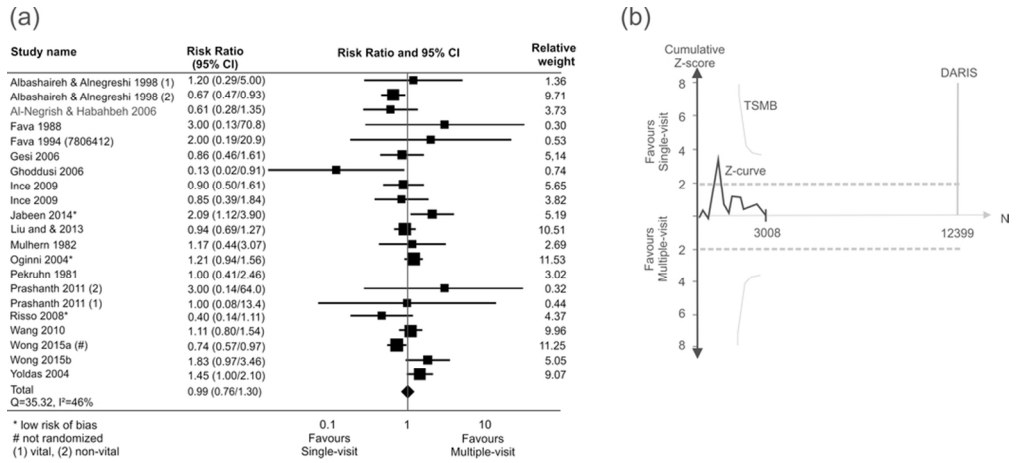

Figure 3: Risk of experiencing any postoperative pain after single- versus multiple-visit root-canal treatment. (a) Forest plot. Low risk of bias and lack of random allocation of treatment is indicated by asterisks and hashtag. Studies which compared treatments in different subgroup of teeth were handled as independent studies and are indicated accordingly. (b) Trial sequential analysis. The information fraction was too small to draw trial sequential futility boundaries.

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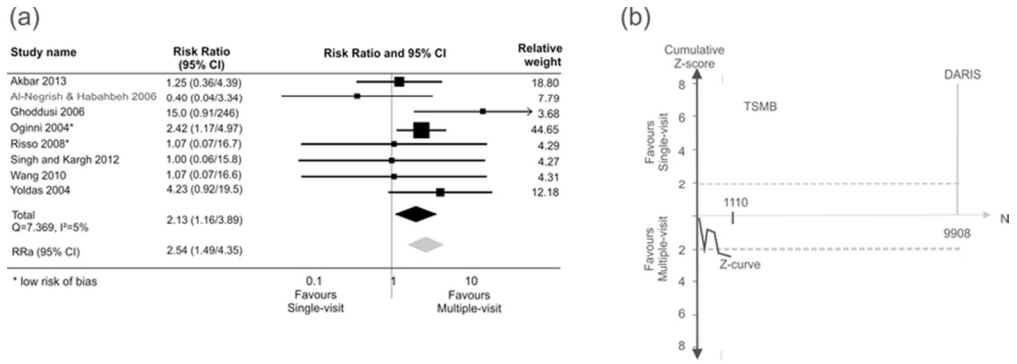

Figure 4: Risk of experiencing flare-up after single- versus multiple-visit root-canal treatment. (a) Forest plot. RR and 95% CI were adjusted for publication bias using trim-and-fill (RRa). Low risk of bias and lack of random allocation of treatment is indicated by asterisks and hashtag. Studies which compared treatments in different subgroup of teeth were handled as independent studies and are indicated accordingly. (b) Trial sequential analysis. The information fraction was too small to draw trial sequential futility boundaries.

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Appendix

Syntheses methods

Unit-of analysis issues were handled as follows: In studies reporting on more than two treatment groups, three approaches were taken to avoid unit-of-analysis conflicts: In case of groups being comparable, we combined them. If additional groups used treatments not in accordance with current standard (e.g. multiple-step treatment without any root-canal medication), this group was omitted. If a factorial design was used (e.g. both groups were compared in vital and non-vital teeth), with separate reporting for all groups, we compared subgroups and handled them as if they were separate studies for meta-analysis.

Meta-regression was additionally performed. As some studies did not clearly state randomization (see above), a sensitivity analysis excluding these studies was performed. Similarly, as some studies reported results to have not been significantly different (but did not report on exact effect estimates), we imputed the number of events per group as the mean event rate in a sensitivity analysis, making best use of all available information. For subgroup comparisons, Chi-square test was performed. For meta-regression, the unrestricted maximum-likelihood method was used; Bonferroni adjustment to correct for multiple testing was planned, but not required, as no significant associations were found even without such correction.

Trial sequential analysis was performed. RIS was calculated based on type I error risk of $\alpha=0.05$ and a type II error risk of $\beta=0.20$ (equivalent to a power of 0.80). The control event proportion (i.e. event incidence in multiple-visit group) and the relative risk reduction (RRR) were used to estimate RIS. RRR was based on an a priori defined worthwhile interventional effect of 20% (lower effects might be worthwhile, but would increase RIS even further) (1, 2). RIS was diversity (heterogeneity) adjusted (DARIS). To assess if differences yielded by conventional meta-analysis are robust, TSA additionally estimates trial sequential monitoring boundaries (TSMB), i.e. statistical thresholds for significance which are adapted depending on the so far reached sample size. The Lan-DeMets version (3) of the O'Brien–Fleming

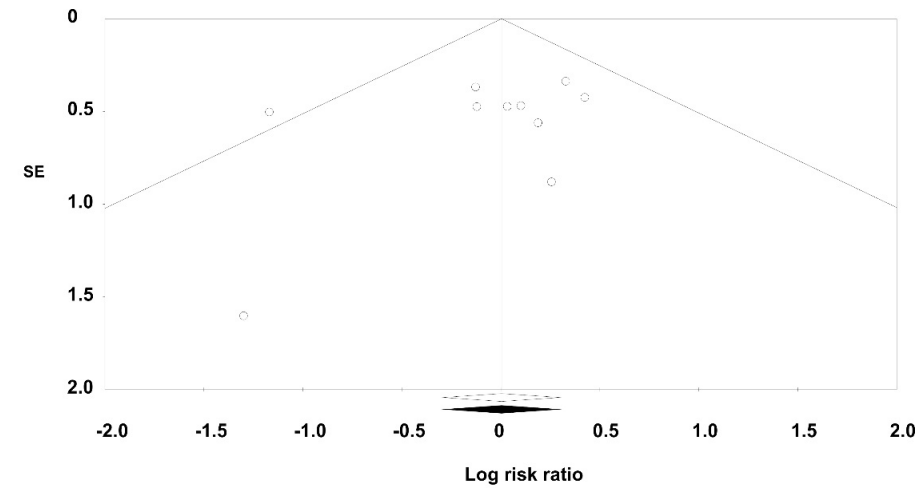
function (4) was used for calculating the TSMBs. In case the cumulative Z-value crossed the conventional boundary of significance (Z=±1.96) but not the TSMBs for benefit or harm, we defined such findings as spuriously significant. Firm evidence was assumed to be reached when the Z-curve crossed the TSMB for benefit or harm before the DARIS was reached. Effect estimates supported by only few small trials are thus handled stricter than those supported by large samples. In addition to such superiority/inferiority TSMBs, monitoring boundaries for futility were calculated (these indicate if further trial conduct is likely to be futile, i.e. if sufficient evidence has been accrued to claim non-inferiority of treatments). Further details regarding the applied method to calculate TSMB have been reported elsewhere (1). TSA was performed with TSA 0.9 (Copenhagen Trial Unit, Copenhagen, Denmark) (5).

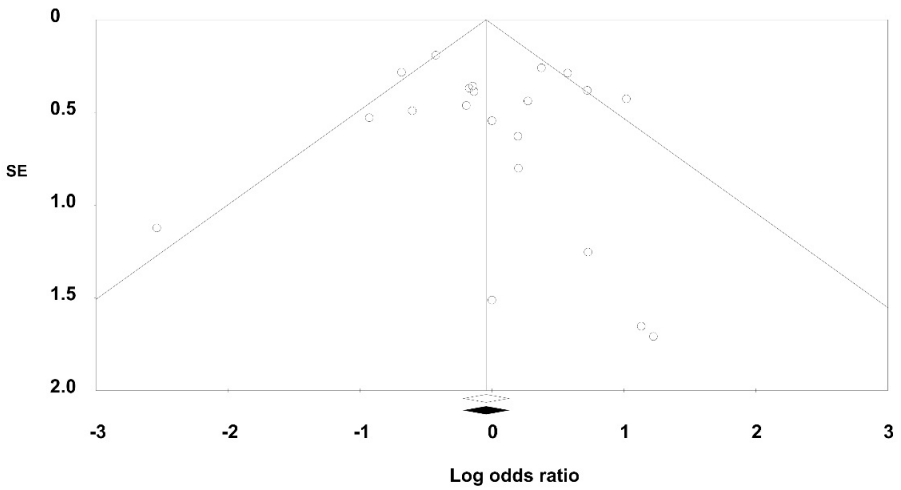
Table S1: Excluded Studies

Soltanoff 1978 (6)	Selection bias (allocation according to tooth status)
O'Keefe 1976 (7)	Selection bias (allocation according to available time)
ElMubarak 2010 (8)	No RCT
Raju 2014 (9)	Did not compare 1- vs 2 visits
Xavier 2013 (10)	No clinical outcome
Bhagwat 2013 (11)	Did not compare 1- vs 2 visits
Roane 1983 (12)	No RCT
Oliet 1983 (13)	Selection bias (allocation according to patient acceptance, available time, symptoms of tooth)
Ether 1978 (14)	Not available
Eleazer 1998 (15)	no RCT
Fava 1989 (16)	Compared different techniques
Fox 1970 (17)	Did not compare 1- vs 2 visits
Genet 1986 (18)	Did not compare 1- vs 2 visits
Morse 1987 (19)	Did not compare 1- vs 2 visits
Yesilsoy 1988 (20)	Did not compare 1- vs 2 visits
Trope 1991 (21)	Did not compare 1- vs 2 visits
Koba 1999 (22)	Did not compare 1- vs 2 visits
Glennon 2004 (23)	Did not compare 1- vs 2 visits
Ng 2004 (24)	no RCT
Georgopoulou 1986 (25)	no RCT
Jurcak 1993 (26)	no RCT
Imura 1995 (27)	no RCT
Walton 1992 (28)	no RCT
Alacam 1985 (29)	Did not compare 1- vs 2 visits
Torabinejad 1994 (30)	Did not compare 1- vs 2 visits
Sjögren 1990 (31)	Did not compare 1- vs 2 visits
Siqueira 2002 (32)	Did not compare 1- vs 2 visits
Orstavik 1996 (33)	Did not compare 1- vs 2 visits
Perkruhn 1986 (34)	Did not compare 1- vs 2 visits
Kvist 2004 (35)	no clinical outcomes reported (CFU)
Rudner 1981 (36)	no RCT
Kenrick 1999 (37)	no RCT
Sjögren 1997 (38)	Did not compare 1- vs 2 visits
Maddox 1977 (39)	Did not compare 1- vs 2 visits
Sjögren 1990 (31)	no RCT
Fleming 2010 (40)	no RCT
Singla 2008 (41)	pulpectomy
Kalhoro 2009 (42)	no RCT
Shaikh 2013 (43)	Not available

Table S2: Risk of bias of included studies. Bias assessment followed guidelines outline by The Cochrane Collaboration (44).

	Sequence generation	Allocation Concealment	Blinding of operator	Blinding of examiner	Incomplete data	Selective reporting	Overall risk of bias
Akbar 2013 (45)	Unclear	Unclear	High	Low	Low	Low	Unclear/High
Albashaireh & Alnegreshi 1998 (46)	Unclear	Unclear	High	Low	Low	Low	Unclear/High
Al-Negrish & Habahbeh 2006 (47)	Unclear	Unclear	High	High	Low	Low	Unclear/High
DiRenzo 2002 (48)	Low	Low	Low	Low	Low	Low	Low
Dorsani 2013 (49)	Unclear	Unclear	High	Low	Low	Low	Unclear/High
Fava 1989 (50)	Unclear	Unclear	High	Low	Low	Low	Unclear/High
Fava 1994 (51)	Unclear	Unclear	High	Low	Low	Low	Unclear/High
Gesi 2006 (52)	Low	Low	High	Low	Low	Low	Unclear/High
Ghoddusi 2006 (53)	Unclear	Unclear	High	Low	Low	Low	Unclear/High
Ince 2009 (54)	Unclear	Unclear	Unclear	Low	Low	Low	Unclear/High
Jabeen 2014 (55)	Low	Low	Low	Low	Low	Low	Low
Liu & Leng 2013 (56)	Unclear	Unclear	High	Low	Low	Low	Unclear/High
Molander 2007 (57)	High	Unclear	High	Low	Low	Low	Unclear/High
Mulhern 1982 (58)	Low	Low	High	Low	Low	Low	Unclear/High
Oginni 2004 (59)	Low	Low	Low	Low	Low	Low	Low
Paredes-Vieyra 2012 (60)	Unclear	High	High	Low	Low	Low	Unclear/High
Pekruhn 1981 (61)	Unclear	Unclear	Unclear	Low	Low	Low	Unclear/High
Penesis 2008 (62)	Low	Low	Low	Low	Low	Low	Low
Peters and Wesslink 2002 (63)	Low	Unclear	High	Low	Low	Low	Unclear/High
Prashanth 2011 (64)	Unclear	High	High	High	High	Low	Unclear/High
Rao 2014 (65)	Unclear	High	Low	Low	Low	Low	Unclear/High
Risso 2008 (66)	Low	Low	Low	Low	Low	Low	Low
Singh and Kargh 2012 (67)	Unclear	High	Low	Low	Low	Low	Unclear/High
Trope 1999 (68), Waltimo 2005 (69)	Low	Low	Low	Low	Low	Low	Low
Wang 2010 (70)	Low	Low	High	High	Low	Low	Unclear/High
Weiger 2000 (71)	Unclear	High	High	Low	Low	Low	Unclear/High
Wong 2015a (72)	High	High	Low	Low	Low	High	Unclear/High
Wong 2015b (73)	Low	Unclear	High	High	Low	Low	Unclear/High
Yoldas 2004 (74)	Unclear	Unclear	High	Low	Low	Low	Unclear/High





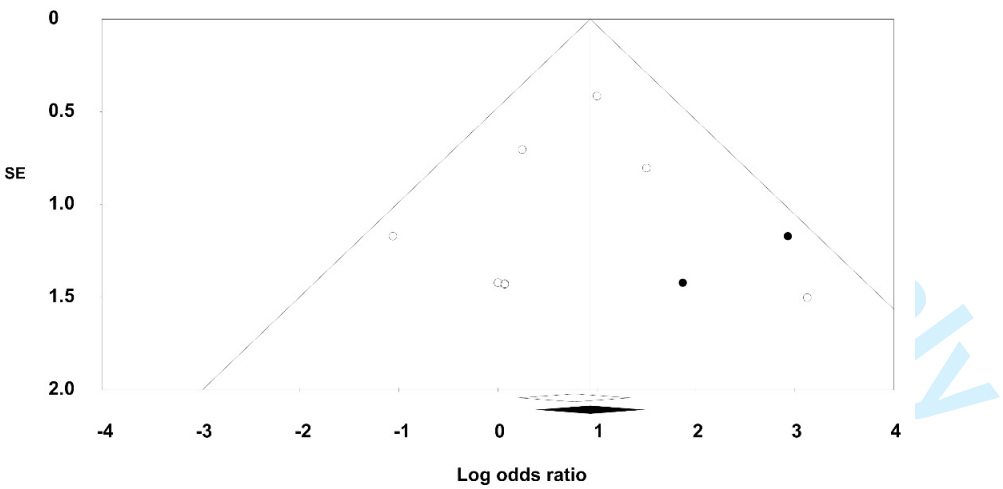


Figure S1: Funnel plots. (a) Risk long-term complications, (b) risk of experiencing any postoperative pain, (c) risk of experiencing a flare-up. Standard errors are plotted against logRR to estimate possible small study effects or publication bias via an asymmetry of the funnel. White circles: estimates reported by included studies, black balls: imputed estimates in case of suspected publication bias. White diamond: effect estimate based on included studies, black diamond: effect estimate based on included and imputed studies.

References for the appendix

1. Schwendicke F, Goestemeyer G, Gluud C. Cavity lining after excavating caries lesions: meta-analysis and trial sequential analysis of randomized clinical trials. *Journal of Dentistry* 2015;**doi: 10.1016/j.jdent.2015.07.017**.
2. Schwendicke F, Karimbux N, Allareddy V, Gluud C. Periodontal treatment for preventing adverse pregnancy outcomes: a meta- and trial sequential analysis. *PloS one* 2015;**10**(6):e0129060.
3. Demets DL, Lan KKG. Interim analysis: The alpha spending function approach. *Statistics in medicine* 1994;**13**(13-14):1341-52.
4. O'Brien PC, Fleming TR. A Multiple Testing Procedure for Clinical Trials. *Biometrics* 1979;**35**(3):549-56.
5. Thorlund K, Engstrøm J, Wetterslev J, Brok J, Imberger G, Gluud C. User Manual for Trial Sequential Analysis (TSA). http://www.ctu.dk/tsa/files/tsa_manual.pdf 2011:1-115.
6. Soltanoff W. A comparative study of the single-visit and the multiple-visit edodontic procedure. *Journal of endodontics* 1978;**4**(9):278-81.
7. O'Keefe EM. Pain in endodontic therapy: preliminary study. *Journal of endodontics* 1976;**2**(10):315-9.
8. El Mubarak AH, Abu-bakr NH, Ibrahim YE. Postoperative pain in multiple-visit and single-visit root canal treatment. *Journal of endodontics* 2010;**36**(1):36-9.
9. Raju TB, Seshadri A, Vamsipavani B, Abhilash K, Subhash AV, Kumari KV. Evaluation of pain in single and multi rooted teeth treated in single visit endodontic therapy. *Journal of international oral health : JIOH* 2014;**6**(1):27-32.
10. Xavier AC, Martinho FC, Chung A, Oliveira LD, Jorge AO, Valera MC, et al. One-visit versus two-visit root canal treatment: effectiveness in the removal of endotoxins and cultivable bacteria. *Journal of endodontics* 2013;**39**(8):959-64.
11. Bhagwat S, Mehta D. Incidence of post-operative pain following single visit endodontics in vital and non-vital teeth: An in vivo study. *Contemporary clinical dentistry* 2013;**4**(3):295-302.
12. Roane JB, Dryden JA, Grimes EW. Incidence of postoperative pain after single- and multiple-visit endodontic procedures. *Oral surgery, oral medicine, and oral pathology* 1983;**55**(1):68-72.
13. Oliet S. Single-visit endodontics: a clinical study. *Journal of endodontics* 1983;**9**(4):147-52.
14. al. ESe. A comparison of one and two visit endodontics. *J Farmacia Odontol* 1978(8):215.
15. Eleazer PD, Eleazer KR. Flare-up rate in pulpally necrotic molars in one-visit versus two-visit endodontic treatment. *Journal of endodontics* 1998;**24**(9):614-6.
16. Fava LR. One-appointment root canal treatment: incidence of postoperative pain using a modified double-flared technique. *International endodontic journal* 1991;**24**(5):258-62.
17. Fox J, Atkinson JS, Dinin AP, Greenfield E, Hechtman E, Reeman CA, et al. Incidence of pain following one-visit endodontic treatment. *Oral surgery, oral medicine, and oral pathology* 1970;**30**(1):123-30.
18. Genet JM, Wesselink PR, Thoden van Velzen SK. The incidence of preoperative and postoperative pain in endodontic therapy. *International endodontic journal* 1986;**19**(5):221-9.
19. Morse DR, Furst ML, Belott RM, Lefkowitz RD, Spritzer IB, Sideman BH. Infectious flare-ups and serious sequelae following endodontic treatment: a prospective randomized

trial on efficacy of antibiotic prophylaxis in cases of asymptomatic pulpal-periapical lesions. *Oral surgery, oral medicine, and oral pathology* 1987;**64**(1):96-109.
20. Yesilsoy C, Koren LZ, Morse DR, Rankow H, Bolanos OR, Furst ML. Post-endodontic obturation pain: a comparative evaluation. *Quintessence international* 1988;**19**(6):431-8.
21. Trope M. Flare-up rate of single-visit endodontics. *International endodontic journal* 1991;**24**(1):24-6.
22. Koba K, Kimura Y, Matsumoto K, Watanabe H, Shinoki T, Kojy R, et al. Post-operative symptoms and healing after endodontic treatment of infected teeth using pulsed Nd:YAG laser. *Endodontics & dental traumatology* 1999;**15**(2):68-72.
23. Glennon JP, Ng YL, Setchell DJ, Gulabivala K. Prevalence of and factors affecting postpreparation pain in patients undergoing two-visit root canal treatment. *International endodontic journal* 2004;**37**(1):29-37.
24. Ng YL, Glennon JP, Setchell DJ, Gulabivala K. Prevalence of and factors affecting post-obturation pain in patients undergoing root canal treatment. *International endodontic journal* 2004;**37**(6):381-91.
25. Georgopoulou M, Anastassiadis P, Sykaras S. Pain after chemomechanical preparation. *International endodontic journal* 1986;**19**(6):309-14.
26. Jurcak JJ, Bellizzi R, Loushine RJ. Successful single-visit endodontics during Operation Desert Shield. *Journal of endodontics* 1993;**19**(8):412-3.
27. Imura N, Zuolo ML. Factors associated with endodontic flare-ups: a prospective study. *International endodontic journal* 1995;**28**(5):261-5.
28. Walton R, Fouad A. Endodontic interappointment flare-ups: a prospective study of incidence and related factors. *Journal of endodontics* 1992;**18**(4):172-7.
29. Alacam T. Incidence of postoperative pain following the use of different sealers in immediate root canal filling. *Journal of endodontics* 1985;**11**(3):135-7.
30. Torabinejad M, Cymerman JJ, Frankson M, Lemon RR, Maggio JD, Schilder H. Effectiveness of various medications on postoperative pain following complete instrumentation. *Journal of endodontics* 1994;**20**(7):345-54.
31. Sjogren U, Hagglund B, Sundqvist G, Wing K. Factors affecting the long-term results of endodontic treatment. *Journal of endodontics* 1990;**16**(10):498-504.
32. Siqueira JF, Jr., Rocas IN, Favieri A, Machado AG, Gahyva SM, Oliveira JC, et al. Incidence of postoperative pain after intracanal procedures based on an antimicrobial strategy. *Journal of endodontics* 2002;**28**(6):457-60.
33. Orstavik D. Time-course and risk analyses of the development and healing of chronic apical periodontitis in man. *International endodontic journal* 1996;**29**(3):150-5.
34. Pekruhn RB. The incidence of failure following single-visit endodontic therapy. *Journal of endodontics* 1986;**12**(2):68-72.
35. Kvist T, Molander A, Dahlen G, Reit C. Microbiological evaluation of one- and two-visit endodontic treatment of teeth with apical periodontitis: a randomized, clinical trial. *Journal of endodontics* 2004;**30**(8):572-6.
36. Rudner WL, Oliet S. Single-visit endodontics: a concept and a clinical study. *Compendium of continuing education in dentistry (Jamesburg, N.J. : 1995)* 1981;**2**(2):63-8.
37. Kenrick S. Endodontics: a multiple-visit or single-visit approach. *Australian endodontic journal : the journal of the Australian Society of Endodontology Inc* 2000;**26**(2):82-5.
38. Sjogren U, Figdor D, Persson S, Sundqvist G. Influence of infection at the time of root filling on the outcome of endodontic treatment of teeth with apical periodontitis. *International endodontic journal* 1997;**30**(5):297-306.

39. Maddox D, Walton R, Davis C. Incidence of posttreatment endodontic pain related to medication and other factors. *Journal of endodontics* 1977;**3**(12):447-52.
40. Fleming CH, Litaker MS, Alley LW, Eleazer PD. Comparison of classic endodontic techniques versus contemporary techniques on endodontic treatment success. *Journal of endodontics* 2010;**36**(3):414-8.
41. Singla R, Marwah N, Dutta S. Single Visit versus Multiple Visit Root Canal Therapy. *International journal of clinical pediatric dentistry* 2008;**1**(1):17-24.
42. Kalhoro FA, Mirza AJ. A study of flare-ups following single-visit root canal treatment in endodontic patients. *Journal of the College of Physicians and Surgeons--Pakistan : JCPSP* 2009;**19**(7):410-2.
43. Shaikh AG, Kalhoro FA, Dall AQ. Evaluation of post operative pain in single and multi visit endodontic therapy with rotary instruments. *Medical Forum Monthly* 2013;**24**(1):49-54.
44. Higgins JPT, Green S, editors. Cochrane Handbook for Systematic Reviews of Interventions. Version 5.10 (updated March 2011): The Cochrane Collaboration; 2011.
45. Akbar I, Iqbal A, Al-Omiri MK. Flare-up rate in molars with periapical radiolucency in one-visit vs two-visit endodontic treatment. *The journal of contemporary dental practice* 2013;**14**(3):414-8.
46. Albashaireh ZS, Alnegrish AS. Postobturation pain after single- and multiple-visit endodontic therapy. A prospective study. *Journal of dentistry* 1998;**26**(3):227-32.
47. Al-Negrish AR, Habahbeh R. Flare up rate related to root canal treatment of asymptomatic pulpally necrotic central incisor teeth in patients attending a military hospital. *Journal of dentistry* 2006;**34**(9):635-40.
48. DiRenzo A, Gresla T, Johnson BR, Rogers M, Tucker D, BeGole EA. Postoperative pain after 1- and 2-visit root canal therapy. *Oral surgery, oral medicine, oral pathology, oral radiology, and endodontics* 2002;**93**(5):605-10.
49. Dorasani G, Madhusudhana K, Chinni SK. Clinical and radiographic evaluation of single-visit and multi-visit endodontic treatment of teeth with periapical pathology: An in vivo study. *Journal of conservative dentistry : JCD* 2013;**16**(6):484-8.
50. Fava LR. A comparison of one versus two appointment endodontic therapy in teeth with non-vital pulps. *International endodontic journal* 1989;**22**(4):179-83.
51. Fava LR. A clinical evaluation of one and two-appointment root canal therapy using calcium hydroxide. *International endodontic journal* 1994;**27**(1):47-51.
52. Gesi A, Hakeberg M, Warfvinge J, Bergenholtz G. Incidence of periapical lesions and clinical symptoms after pulpectomy--a clinical and radiographic evaluation of 1- versus 2-session treatment. *Oral surgery, oral medicine, oral pathology, oral radiology, and endodontics* 2006;**101**(3):379-88.
53. Ghoddusi J, Javidi M, Zarrabi MH, Bagheri H. Flare-ups incidence and severity after using calcium hydroxide as intracanal dressing. *The New York state dental journal* 2006;**72**(4):24-8.
54. Ince B, Ercan E, Dalli M, Dulgergil CT, Zorba YO, Colak H. Incidence of postoperative pain after single- and multi-visit endodontic treatment in teeth with vital and non-vital pulp. *European journal of dentistry* 2009;**3**(4):273-9.
55. Jabeen S, Khurshiduzzaman M. Incidence of post obturation pain following single and multi visit root canal treatment in a teaching hospital of Bangladesh. *Mymensingh medical journal : MMJ* 2014;**23**(2):254-60.
56. Liu S, Leng Z-y. Short-term clinical effect of single-visit root-canal therapy in infected root canals. *Journal of Shanghai Jisobong University* 2013;**33**(7):1014-17.

57. Molander A, Warfvinge J, Reit C, Kvist T. Clinical and radiographic evaluation of one- and two-visit endodontic treatment of asymptomatic necrotic teeth with apical periodontitis: a randomized clinical trial. *Journal of endodontics* 2007;**33**(10):1145-8.
58. Mulhern JM, Patterson SS, Newton CW, Ringel AM. Incidence of postoperative pain after one-appointment endodontic treatment of asymptomatic pulpal necross in single-rooted teeth. *Journal of endodontics* 1982;**8**(8):370-5.
59. Oginni A, Udoye CI. Endodontic flare-ups: comparison of incidence between single and multiple visits procedures in patients attending a Nigerian teaching hospital. *Odonto-stomatologie tropicale = Tropical dental journal* 2004;**27**(108):23-7.
60. Paredes-Vieyra J, Enriquez FJ. Success rate of single- versus two-visit root canal treatment of teeth with apical periodontitis: a randomized controlled trial. *Journal of endodontics* 2012;**38**(9):1164-9.
61. Pekruhn RB. Single-visit endodontic therapy: a preliminary clinical study. *Journal of the American Dental Association (1939)* 1981;**103**(6):875-7.
62. Penesis VA, Fitzgerald PI, Fayad MI, Wenckus CS, BeGole EA, Johnson BR. Outcome of one-visit and two-visit endodontic treatment of necrotic teeth with apical periodontitis: a randomized controlled trial with one-year evaluation. *Journal of endodontics* 2008;**34**(3):251-7.
63. Peters LB, Wesselink PR. Periapical healing of endodontically treated teeth in one and two visits obturated in the presence or absence of detectable microorganisms. *International endodontic journal* 2002;**35**(8):660-7.
64. Prashanth MB, Tavane PN, Abraham S, Chacko L. Comparative evaluation of pain, tenderness and swelling followed by radiographic evaluation of periapical changes at various intervals of time following single and multiple visit endodontic therapy: an in vivo study. *The journal of contemporary dental practice* 2011;**12**(3):187-91.
65. Rao KN, Kandaswamy R, Umashetty G, Rathore VP, Hotkar C, Patil BS. Post-Obturation pain following one-visit and two-visit root canal treatment in necrotic anterior teeth. *Journal of international oral health : JIOH* 2014;**6**(2):28-32.
66. Risso PA, Cunha AJ, Araujo MC, Luiz RR. Postobturation pain and associated factors in adolescent patients undergoing one- and two-visit root canal treatment. *Journal of dentistry* 2008;**36**(11):928-34.
67. Singh S, Garg A. Incidence of post-operative pain after single visit and multiple visit root canal treatment: A randomized controlled trial. *Journal of conservative dentistry : JCD* 2012;**15**(4):323-7.
68. Trope M, Delano EO, Orstavik D. Endodontic treatment of teeth with apical periodontitis: single vs. multivisit treatment. *Journal of endodontics* 1999;**25**(5):345-50.
69. Waltimo T, Trope M, Haapasalo M, Orstavik D. Clinical efficacy of treatment procedures in endodontic infection control and one year follow-up of periapical healing. *Journal of endodontics* 2005;**31**(12):863-6.
70. Wang C, Xu P, Ren L, Dong G, Ye L. Comparison of post-obturation pain experience following one-visit and two-visit root canal treatment on teeth with vital pulps: a randomized controlled trial. *International endodontic journal* 2010;**43**(8):692-7.
71. Weiger R, Rosendahl R, Lost C. Influence of calcium hydroxide intracanal dressings on the prognosis of teeth with endodontically induced periapical lesions. *International endodontic journal* 2000;**33**(3):219-26.
72. Wong AW, Zhang S, Li SK, Zhu X, Zhang C, Chu CH. Incidence of post-obturation pain after single-visit versus multiple-visit non-surgical endodontic treatments. *BMC oral health* 2015;**15**:96.

73. Wong AW, Tsang CS, Zhang S, Li KY, Zhang C, Chu CH. Treatment outcomes of single-visit versus multiple-visit non-surgical endodontic therapy: a randomised clinical trial. *BMC oral health* 2015;**15**(1):162.
74. Yoldas O, Topuz A, Isci AS, Oztunc H. Postoperative pain after endodontic retreatment: single- versus two-visit treatment. *Oral surgery, oral medicine, oral pathology, oral radiology, and endodontics* 2004;**98**(4):483-7.

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	3
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	3
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	5-6
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	6
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	6
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	6-7
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	7
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Fig 1
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	Fig 1
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	8
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	8
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	9
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	9-10
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	9-10

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	9-10
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	9-10
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	Fig 1
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	Tab. 1
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	Tab. S2
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	Fig. 2-4
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	Fig. 2-4
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	Tab S2
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	Fig 2-4
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	13-15
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	15-16
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	16-17
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	17

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

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