Emergency Management of Acute Apical Periodontitis in the Permanent Dentition: A Systematic Review of the Literature

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Abstract

Objective: *To perform a systematic literature review and meta-analysis on the effectiveness of interventions used in the emergency management of acute apical periodontitis in the permanent dentition.*

Methods: *Electronic databases were searched from their inception to 2001. These searches, combined with manual searching, yielded 1,097 citations, of which 92 were relevant. Independent application of inclusion criteria by 2 teams of reviewers yielded 15 eligible randomized controlled trials. Data on population, interventions, outcomes (pain relief or change in intensity of pain as reported by patients or clinicians) and methodological quality were determined by independent duplicate review. Disagreements were resolved by consensus.*

Results: *Meta-analysis showed that pre-emptive analgesics (nonsteroidal anti-inflammatory drugs [NSAIDs]) in conjunction with pulpectomy provided a significant benefit (weighted mean difference –11.70, 95% confidence interval –22.84 to –0.56). Three interventions did not show significant benefit: systemic antibiotics, intracanal treatment with a steroid–antibiotic combination, and trephination through attached gingiva.*

Conclusions: *In the management of pain associated with acute apical periodontitis, there is strong evidence to support the use of systemic NSAIDs in conjunction with nonsurgical endodontics. The use of antibiotics is not recommended.*

MeSH Key Words: *endodontics; meta-analysis; periapical periodontitis; toothache*

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Acute apical periodontitis (AAP) is an inflammatory condition of the periapical tissues of the periodontium, usually resulting from irreversible pulpitis and pulpal necrosis. Although chemical and physical factors can cause pulpitis, most cases have a microbial cause, usually secondary to caries or trauma.[1] Although the presence of some bacteria in the periapical region of an affected tooth has been demonstrated,[2] AAP is predominantly an inflammatory, rather than an infectious, process.

Patients with AAP often have moderate to severe pain, which results in the need for emergency treatment.[3] Because the transition from inflamed pulp to necrotic pulp to acute periapical disease occurs along a continuum, not all of the signs and symptoms, as described below, will be present in all patients. Patients with AAP usually present with dull, throbbing, constant pain; absence of swelling; a negative or delayed positive result on vitality testing; absence of thermal sensitivity of the tooth; and pain on biting or percussion.[4] Radiographic changes such as widening of the periodontal ligament may be present, but frank radiolucency will not be observed.

Because of the progression from inflamed pulp to AAP, the diagnosis is not always straightforward. Vitality tests are affected by a number of factors, including the amount of residual pulp in the periapical area and the size of any restoration on the tooth.[5] Sensitivity of the tooth to thermal changes may be due to recession,[6] occlusal trauma, orthodontic movement or sinusitis.[7] Tooth pain may also be referred from other orofacial structures or sites distant from the tooth.[8] A misdiagnosis may lead to inappropriate treatment.

Although toothache is a subjective symptom, it can have a significant social impact.[9] Emergency dental treatment accounts for 2% to 6% of the costs of all dental therapy, an amount similar to all periodontal treatment costs.[10] The prevalence of perceived toothache is difficult to determine. Most epidemiologic research combines pain from a tooth with pain from oral lesions and temporomandibular dysfunction. There are no data on the prevalence of AAP specifically. Toothache itself is rarely defined in the literature, which means the pain may be from any of these sources or of non-odontogenic origin. The prevalence of toothache is reported to range from 12%[11] to 50%.[12] It is reported more frequently in men and in lower socioeconomic groups.

Because AAP is due to pulpal death, the recommended treatment is relief of the inflammatory pressure in the periapical area. This is usually accomplished via access through the tooth and extirpation of the necrotic pulp (i.e. pulpectomy).[4] Other therapies, including systemic or local medicaments such as corticosteroids, analgesics and antibiotics, have been used on their own or in conjunction with pulpectomy. The pain associated with AAP is not the result of an infectious process, so the use of antibiotics may be questionable. Nonetheless, up to 75% of patients with painful pulpitis are treated with antibiotic therapy.[13–15]

In view of the prevalence of this condition in everyday practice and the anecdotal evidence of practice variation, a systematic review is warranted. The objective of this review is to determine the effectiveness of the various interventions used in the management of AAP in the permanent dentition.

Prior Reviews

Before this review was initiated, the MEDLINE database and the Cochrane Library were searched for the period 1991 to 2001. The terms "apical periodontitis," "pulpitis," "toothache" and "emergency care," with limitations of human studies published in English and application of "review articles" as a publication-type limit, were used in an attempt to locate systematic reviews related to this topic. No other reviews were identified.

Methods

Study Identification

To identify relevant clinical trials, the MEDLINE and EmBase databases and the Controlled Trials Register of the Cochrane Library were searched from their time of inception to August 2001. A further search of the Specialized Register of Clinical Trials of the Cochrane Oral Health Group was also performed. The search strategy for nonsteroidal anti-inflammatory drugs (NSAIDs) in the management of AAP is outlined in Appendix 1. This search was repeated for all reasonable interventions. Pharmacotherapeutics included systemic therapy (antibiotics, corticosteroids, and NSAIDs or analgesics) and local therapy (irrigants, intracanal medicaments). Surgical measures encompassed the establishment of drainage either through the tooth (pulpectomy, open or closed) or bone (trephination). Extraction, occlusal adjustment and no treatment were also investigated; however, for these interventions, either no evidence was available for analaysis, the outcomes did not fit the eligibility criteria, or the data were not suitable for analysis.

Titles and abstracts, where available, were examined by 2 reviewers, and all papers deemed relevant or possibly relevant by either reviewer were obtained. The reference lists of all retrieved articles, review papers and relevant book chapters were scanned, and pertinent citations identified in this manner were obtained. After the study selection process described below, endodontic experts and published authors were contacted and asked to provide further references that the search might have missed. To assess the proportion and possible impact of non-English citations, no citations were excluded from the list of relevant papers on the basis of language. However, the full text was obtained only for papers published in English or French. Throughout the project, an ongoing literature search was carried out. Unpublished studies were not sought.

Study Selection

The following criteria were used to determine eligibility of studies for inclusion in the review.

Target Population: Patients presenting with AAP resulting from nonvital pulp in the permanent dentition. Given the variation in the definition of AAP in the endodontic literature, for the purposes of this review the condition was considered to be characterized by dull, throbbing, constant pain; absence of swelling; a negative or delayed positive result on vitality testing; absence of thermal sensitivity; pain on biting or percussion; and presence or absence of radiographic changes (such as widening of the periodontal ligament space but not periapical radiolucency).

Interventions: Systemic and local pharmacotherapeutics, local surgical measures, occlusal adjustment, no treatment, extraction.

Outcome Measures: The effect on patient outcomes in terms of symptom relief as measured by patients or clinicians.

Types of Studies: Randomized controlled trials and controlled clinical trials that met the eligibility criteria.

The eligibility criteria were tested, and reviewers were trained on a small sample of papers, in a pilot test, before the start of the formal study. Two teams of 2 reviewers then explicitly applied the criteria to the studies retrieved, with each team reviewing half of the selected papers. Within each team, the 2 reviewers assessed the papers independently. Agreement on eligibility was measured with the

Table 1 **Quality Assessment Scale (adapted from Jadad and others[16])**

Question	Answer[a]	Points
1. Was the study described as randomized (this includes use of words such as "randomly," "random" and "randomization")?	**No**	0
	Yes	1
	Yes, and the method to generate the sequence of randomization was **described and it was appropriate** (table of random numbers, computer generated, etc.)	2
	Yes, and the method to generate the sequence of randomization was **described and it was inappropriate** (patients were allocated alternately or according to date of birth, hospital number, etc.)	0
2. Was the study described as double-blind?	**No**	0
	Yes	1
	Yes, and the method of double blinding was **described and appropriate** (identical placebo, active placebo, dummy, sham)	2
Or, if double-blinding was not appropriate to the nature of the study, was the study described as blinded?	**No**	0
	Yes	1
	Yes, and the person evaluating the outcome was blinded to the **treatment allocation of the patient**	2
3. Was there a description of withdrawals and dropouts?	**No**	0
	Yes	1
Total possible score		**5**

[a]*For each question, pick only the best answer and circle the points for that question.*

kappa statistic, which corrects for chance agreement. The reviewers then discussed reasons for disagreement to reach consensus.

Assessment of Methodological Quality

Two reviewers used a checklist to independently assess the methodological quality of all selected studies. The checklist addressed whether the population, intervention(s), outcomes and study design were described clearly. In addition, the validated assessment tool developed by Jadad and others[16] (the Quality Assessment Scale) was used to assign a score to the quality of controlled trials, as described in Table 1. The maximum possible score was 5.

Data Extraction

Pertinent information was abstracted from each study, including study design and sample size, population (including the study setting), patient characteristics and eligibility criteria, interventions and comparisons used (including dose, schedule and route of drugs, or specifics of the technique; co-interventions were allowed), outcome measures and results.

There was considerable variation among the studies in the schedules for patient evaluation, which made it impossible to extract data for the same time frame for each study. Instead, the most comparable time frames were chosen, taking into consideration the pharmacokinetics of the particular drug and the timing of local anesthetic, if used.

For papers published within the past 15 years for which data were missing or unclear, the authors were contacted and asked to provide detailed information.

Data Analysis

Potential sources of variability among the included studies in terms of the population, exposures, outcomes and methods were identified. Within each category of intervention, trials that were not too clinically different (i.e., not too heterogeneous) were pooled and evaluated statistically by means of meta-analytic techniques.

SPSS 11.0 for Windows (SPSS Inc., Chicago, Ill.) was used to calculate the kappa statistic. RevMan 4.1 for Windows (Cochrane Collaboration, Oxford, UK) was used to perform the meta-analysis.

Meta-analysis

The outcomes of interest were relief of pain or change in intensity of pain as assessed by patients or clinicians. These data were summarized for all studies for which they were available. For outcomes reported as binary data, individual odds ratio (OR) of response to treatment (test versus control) and associated 95% confidence intervals were calculated for each trial. For outcomes reported as continuous data, individual weighted mean differences (WMD) were calculated for each study. When calculating the combined mean effect of treatment from several studies, this method gives greater weight to studies with larger sample sizes. Where different numeric scales were used by different researchers, data were transformed to a common percentage scale, by means of the method described by Eisenberg and others,[17] according to the following formula: (reported value of scale) / (scale maximum value – scale minimum value) × 100 = value (%). A pooled interval estimate of the population OR or WMD was calculated. Heterogeneity was assessed with the chi-square test.

Table 2 **Reasons for exclusion of 68 studies**

Reason	No. of studies
Wrong population	43
Wrong study type (case series, review or letter)	10
Wrong outcome measure	11
Data not usable	4

Significance for this test was set liberally at $p \leq 0.1$, since, in practice, the test often lacks the power to detect interstudy differences of treatment effect.[18] The DerSimonian and Laird Random Effects Model of pooling[19] was used, on the assumption of the presence of interstudy variability, to provide a more conservative estimate of the true effect.

Several sources of heterogeneity were anticipated. To explore the relationship between treatment effect and study features, several a priori hypotheses regarding heterogeneity were developed and subgroup analyses planned. A separate analysis was proposed for each intervention, if there were sufficient studies (more than one) for pooling within each category. Subgroup analyses were also planned for studies that examined analgesics given to relieve pain in the preoperative period, analgesics given to relieve pain in the post-operative period and analgesics given pre-emptively in the preoperative period to relieve post-operative pain. A sensitivity analysis was planned to evaluate the influence of methodological quality (score ≥ 3 versus score < 3).

Results

Study Identification and Selection

In total, 1,097 English- and French-language studies were identified by the search. (Twenty-one reports in languages other than English or French were retrieved but were not reviewed because of lack of resources for translation.) Ninety-two of the 1,097 papers met the broad screening criteria and were retrieved and reviewed. Upon closer scrutiny by the 2 teams of reviewers, a further 68 studies (including 12 papers in French) were eliminated because they did not meet the inclusion criteria. The reasons for exclusion are shown in Table 2. References for these excluded studies are listed in Appendix 2.

Agreement on eligible studies between the 2 reviewers in each of the 2 groups was high (0.60 and 0.86), and the kappa value was fair (kappa = 0.41 and 0.21). Discrepancies were due to oversights on the part of one of the reviewers or unclear reports. These were resolved by consensus. The low kappa scores may have been influenced by the large number of rejected papers compared with the small number of accepted papers.

For the remaining 24 papers, 15 authors were contacted for clarification or verification of the population, intervention or outcome. Thirteen responded, and on the basis of the information provided, 10 additional papers were excluded and one study not found in the original search was included.

Trial Characteristics

A total of 15 papers,[20–34] all randomized controlled trials, met all eligibility criteria. A total of 1,115 patients were included in the 15 studies. Grouped by intervention, 8 studies dealt with systemic pharmacotherapeutics, 3 with intracanal medicaments, 3 with surgical measures and 1 with occlusal reduction. The salient features of the trials are shown in Table 3.

Methodological Quality

The median quality score was 3 (range 1–5). Five studies were of low quality (score 1 or 2), 2 studies had a score of 3, 7 studies had a score of 4, and 1 study had a score of 5 (Table 3). Although all studies stated that they were randomized, only 3 described the method of randomization.[23,24,29] Twelve of the studies were described as double blind, with the method of blinding clearly appropriate in 11.[21,23–26,28–32,34] Four of the 15 provided a statement on withdrawals and dropouts;[23,25,30,34] this information was obtained for 2 more studies by means of author contacts.[21,32] Agreement for the quality of studies was modest (kappa = 0.43). Disagreements were related both to oversights and to subjective interpretation of unclear reports. The final scores represent consensus between the 2 reviewers.

Meta-analysis

Of the 15 included trials, 5 provided continuous data that could be analyzed for the outcome "mean pain relief"[20,21,23,30,32] and 4[25–27,34] provided insufficient information (means but no standard deviations) for statistical analysis. One trial[32] studied the effect of an NSAID or local anesthetic injected intraorally or intramuscularly, 30 minutes preoperatively, on both preoperative and post-operative pain. The 2 sets of data in this study were separated for the purpose of this analysis.

Eight trials[22–25,28–31] reported relevant binary data on the outcome of intensity of pain (proportions of patients in the treatment and control groups experiencing clinically acceptable pain; i.e., no or mild pain) after administration of the intervention or comparison. Four trials[26,27,33,34] did not report any usable continuous or binary data for the outcome of interest and could not be included in either analysis. Subgroup analysis was not possible for antibiotics or postoperative use of analgesics or anti-inflammatory drugs, as there was only one study in each of those categories.

Outcome: Mean Pain Relief

The results for the 5 studies that provided continuous data are shown in Fig. 1. When all interventions were included in the analysis, there was a significant treatment effect (WMD –22.70; 95% confidence interval [CI] –36.20 to –9.21). There was significant heterogeneity of the results of the individual studies (chi-square = 219.15, $p < 0.00001$), which was expected, given the diversity of the interventions.

Table 3 Features of 15 included trials

Study (and quality score)	No. of patients analyzed	Pain scale used	Baseline pain intensity[a]	Intervention	Comparison	Endodontic therapy	Follow-up period
Systemic pharmacotherapeutics							
Curtis and others[20] (1)	40	100 mm VAS	Severe	Ketorolac 60 mg IM	Placebo	None	90 minutes
Penniston and Hargreaves[32] (4[b])	52	100 mm VAS[c]	Moderate	Ketorolac 30 mg IM or infiltration 60 minutes pre-op	Placebo IM or infiltration; mepivicaine 2% + vasoconstrictor infiltration	Pulpotomy	6 hours
[d]Sadeghein and others[34] (4)	63	10 cm VAS	Severe	Ketorolac 10 mg po 90 minutes pre-op	Acetaminophen 325 mg/codeine 15 mg	"Appropriate dental treatment to eliminate pain"	90 minutes
Flath and others[23] (5)	120[e]	100 mm VAS[c]	Moderate	Flurbiprofen 100 mg po 30 minutes pre-op	Placebo	Pulpectomy/ debridement	24 hours
Doroschak and others[21] (4[b])	49	100 mm VAS[c]	Moderate to severe	Post-op flurbiprofen 100 mg loading dose then 50 mg q6h × 2 days po or tramadol 100 mg/ 50 mg po as above or flurbiprofen 100 mg/ 50 mg + tramadol 100 mg/50 mg po as above	Placebo	Pulpectomy/ debridement	2 days
[d]Liesinger and others[26] (3)	106	9-point categorical scale	Moderate	Post-op dexamethasone IM at 2, 4, 6 or 8 mg/mL	Placebo	Pulpectomy/ debridement ± obturation	5 days
Krasner and Jackson[25] (4)	48	100-point scale	Low to moderate	Post-op dexamethasone 2.25 mg po loading dose and 0.75 mg q3h × 4 doses	Placebo	Pulpectomy/ debridement	24 hours
Nagle[29] (4)	40	4-point categorical scale	Moderate to severe	Penicillin VK 500 mg po q6h × 7 days	Placebo	None until day 7, then pulpectomy	7 days
Local pharmacotherapeutics							
Moskow and others[28] (2)	50	100-point scale, reported as 4 categories	36/50 patients had moderate to severe	Dexamethasone 4 mg/mL solution	Placebo	Pulpectomy/ debridement	72 hours
Negm[30] (4)	393	4-point categorical scale	Moderate	NSAID (ketoprofen or diclofenac)	Placebo	Pulpectomy/ debridement	3 days
Fava[22] (1)	48 patients, 60 teeth	Unclear	Not stated	Corticosteroid–antibiotic solution (Otosporin)	Calcium-hydroxide paste (Calen)	Pulpectomy/ debridement	7 days
Occlusal adjustment							
[d]Rosenberg and others[33] (1)	53 teeth	Unclear	Not stated	Occlusal reduction	Simulated or no reduction	Endodontic therapy	48 hours

Table 3 **continued**

Study (and quality score)	No. of patients analyzed	Pain scale used	Baseline pain intensity[a]	Intervention	Comparison	Endodontic therapy	Follow-up period
Trephination							
[d]Moos and others[27] (1)	17	100 mm VAS	Severe	Pulpectomy + gingival incision and trephination with #4 round bur, slow-speed handpiece	Pulpectomy alone	Pulpectomy + calcium-hydroxide paste	6 days
Houck and others[24] (4)	50	4-point categorical scale	Mild to moderate	Pulpectomy + trephination with Stabident perforator through bone at level of attached gingiva	Pulpectomy + mock trephination	Pulpectomy/ debridement	7 days
Nist and others[31] (3)	50	4-point categorical scale	Not stated	Pulpectomy + trephination with Stabident perforator through bone at level of attached gingiva	Pulpectomy + mock trephination	Pulpectomy/ debridement	7 days

VAS = Visual Analog Scale, IM = intramuscular, po = by mouth, NSAID = nonsteroidal anti-inflammatory drug.
[a]Pain intensity: mild < 30/100; moderate 30–69/100; severe < 70/100
[b]Quality score upgraded from 3, based on information from author.
[c]More than one scale was used in study; 100-mm VAS results were used in the present analysis.
[d]Unable to abstract useable data.
[e]There were a total of 120 patients in the study, of whom 56 were symptomatic on entry. Data for these patients were analyzed separately in the study and therefore could be included in the meta-analysis reported here.

Thus, there is no overlap in confidence intervals for 2 of the studies, Curtis and others[20] and Negm[30] (Fig. 1).

When the low-quality trial (Quality Assessment Score of 2 or less) was excluded in a sensitivity analysis, the significant benefit of the treatments did not persist, although a trend toward treatment effectiveness (Fig. 2) was still observed.

Results of the subgroup analyses for "mean pain relief" are shown in Table 4. There was a statistically significant difference when pre-emptive or immediate preoperative analgesia was used (WMD –11.70, 95% CI –22.84 to –0.56). There was a nonsignificant trend toward a difference between treatment and control when analgesics were used for adequate pain relief before (or in lieu of) definitive endodontic therapy.

Outcome: Intensity of Pain

The combined results of the ORs of the 8 studies that reported data for the outcome "intensity of pain" are shown in Fig. 3. The combined results suggest a trend for a difference in the treatment of pain between treatment and control groups (OR 0.48, 95% CI 0.18 to 1.27), but statistical significance was not achieved. Significant heterogeneity of the results of the studies was evident (chi-square = 34.47, $p < 0.00001$). A separate analysis excluding low-quality trials did not substantially affect the results. Results of the subgroup analyses for "proportion of patients with no or mild pain" are shown in Table 5. Although a trend toward effectiveness was demonstrated in all subgroups, no intervention was statistically significant.

The test for heterogeneity showed considerable variation in the results for the anti-inflammatory subgroups (one trial studied an NSAID, the other a corticosteroid). The test for heterogeneity was nonsignificant for the intracanal medicament and trephination subgroups, indicating that there was no substantial variation in the results of these trials.

Discussion

In this overview, a systematic review[35] was used to assemble and synthesize evidence from the international literature on interventions used in the management of AAP and to evaluate the effectiveness of those interventions. The results of the meta-analysis suggest that, overall, current interventions used in endodontic therapy are effective in relieving pain associated with AAP and that pre-emptive analgesia, in conjunction with nonsurgical endodontic therapy, provides significant benefit. Other subgroups of pooled interventions, given in addition to definitive pulpal therapy, showed nonsignificant trends in favour of treatment. For the outcome "mean pain relief," all individual studies showed either a significant benefit or a positive trend favouring the particular intervention. When primary studies that reported the proportion of patients achieving no or mild pain were examined, 3 interventions (intracanal treatment with a steroid–antibiotic combination, trephination through attached gingiva and systemic antibiotics) showed

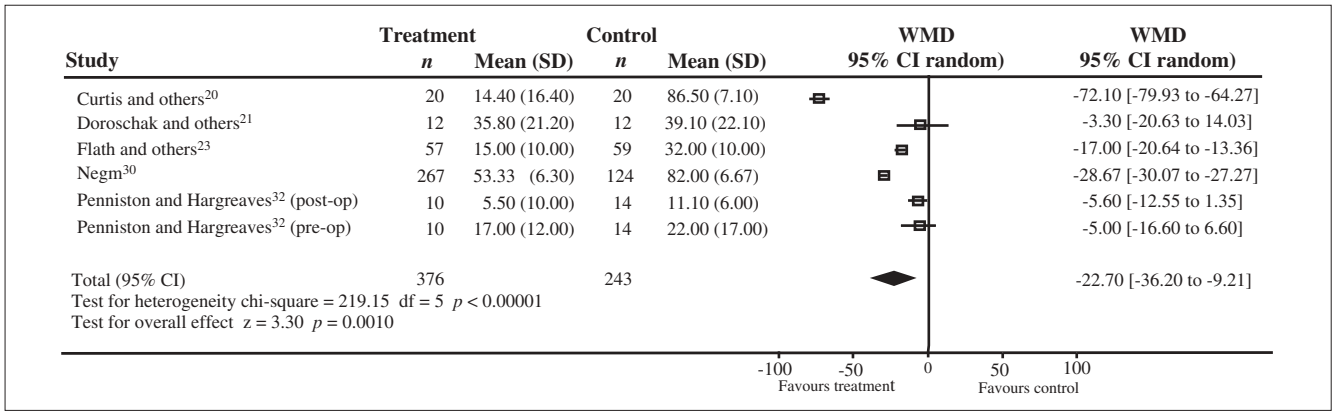

Figure 1: *Results of the meta-analysis (all interventions) for the outcome mean pain relief, at comparable follow-up times. SD = standard deviation, WMD = weighted mean difference, CI = confidence interval, df = degrees of freedom.*

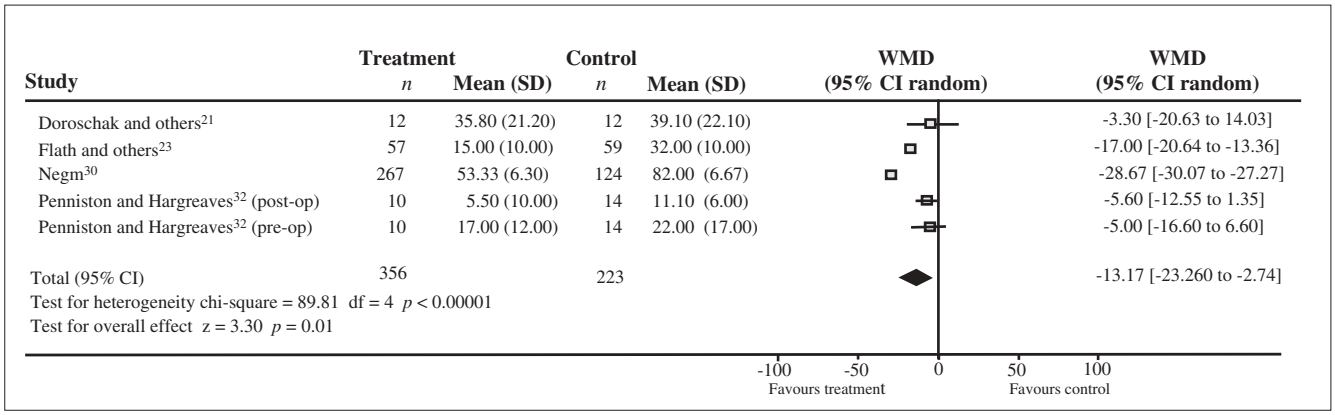

Figure 2: *Results for the sensitivity analysis for the outcome mean pain relief. SD = standard deviation, WMD = weighted mean difference, CI = confidence interval, df = degrees of freedom.*

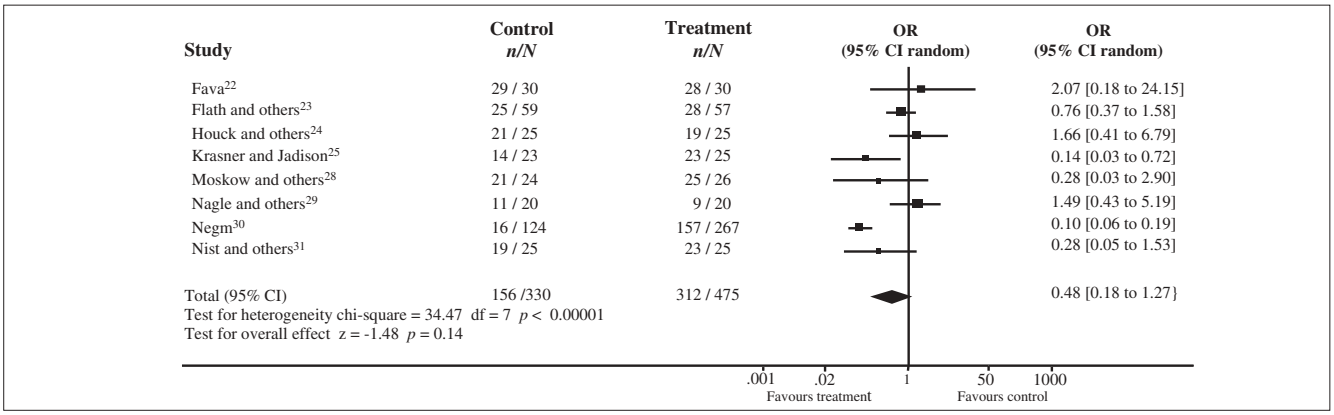

Figure 3: *Results of the meta-analysis (all interventions) for the outcome intensity of pain (proportion of patients achieving no or mild pain status) after the intervention at comparable follow-up times. OR = odds ratio, CI = confidence interval, df = degrees of freedom.*

Understanding meta-analysis graphs (Figs. 1–3)

For each individual study, the box represents the study result or point estimate (weighted mean difference for continuous data, odds ratio for dichotomous data), which is the best estimate of the true value for the population from which the sample of patients was taken. The horizontal bars on either side of the point estimate represent the 95% confidence interval, which is the uncertainty due to chance associated with the estimate; the true result may lie anywhere within that interval. Wide confidence intervals indicate a large amount of uncertainty about the estimate. Narrow confidence intervals lead to greater confidence that the estimate is close to the true result — there is greater precision associated with the result. The vertical line is the line of equivalence, where there is no difference between the effect of the treatment and the effect of the control. A point estimate that lies on the "favours treatment" side of the vertical line indicates that the intervention may be beneficial; one that lies on the "favours control" side indicates that the control or placebo may actually be more beneficial than the treatment being studied. However, if the confidence interval for the estimate crosses the vertical line of the graph, one of the possible values for the true estimate is zero. In this situation, the result is deemed to be not statistically significant. The diamond at the lower end of the graph represents the combined results of all studies and its associated 95% confidence interval.

Table 4 **Results of subgroup analysis for outcome "mean pain relief"**

Intervention	No. of studies (reference)	No. of patients	WMD (and 95% CI)
Preoperative analgesia	2 (Curtis and others,[20] Penniston and Hargreaves[32])	64	–38.69 (–104.5 to 27.07)
Pre-emptive analgesia[b]	2 (Flath and others,[23] Penniston and Hargreaves[32])	140	–11.70 (–22.84 to –0.56)[a]

WMD = weighted mean difference, CI = confidence interval.
[a]*Statistically significant.*
[b]*Thirty to 60 minutes before local anesthesia and pulpectomy.*

Table 5 **Results of subgroup analysis for outcome "proportion of patients with no or mild pain"**

Intervention	No. of studies (references)	No. of patients	Time after surgery	Odds ratio (and 95% CI)
Anti-inflammatory drugs	2 (Flath and others,[23] Krasner and Jackson[25])	164	7–8 hours	0.22 (0.01–4.00)
			24 hours	0.38 (0.07–2.01)
Intracanal medicaments	3 (Fava,[22] Moskow and others,[28] Negm[30])	501	48 hours	0.29 (0.05–1.66)
Trephination	2 (Houck and others,[24] Nist and others[31])	100	24 hours	0.51 (0.09–2.74)
			Day 3	0.72 (0.12–4.19)
			Day 5	6.83 (0.78–59.81)

CI = confidence interval.

a nonsignificant trend favouring the control group. This result suggests that these are not effective choices in the management of pain associated with AAP. For systemic antibiotics, this makes biologic sense, given the absence of blood circulation within necrotic pulp. Because antibiotics cannot reach and eliminate microorganisms present in the root canal system, the source of the problem is unaffected by systemic antibiotic therapy.[1]

The results of these analyses must be interpreted with caution. By pooling the results of a number of studies, meta-analysis can increase the statistical power of the combination of studies to detect a treatment effect if one truly exists, even though individual studies may not detect the effect. However, a pool of a scant number of small trials (especially in a subgroup analysis) may still be underpowered to detect an effect. Most of the studies in this review had 60 or fewer patients, and only one study reported a power-based sample size calculation. Furthermore, the quality of reporting and the inability to obtain vital information (particularly related to outcome data) from some authors, led to the omission of some studies that otherwise might have been included. This problem was compounded by inconsistencies in research designs, unclear definitions of disease entities and reporting of multiple outcome measures. In some studies, the rationale for including patients was unclear. For example, where the outcome measure was related to pain relief, patients were included who had no or mild pain at baseline. A few studies used teeth, rather than patients, as the unit of analysis. For measurement of a patient outcome such as pain, this is clearly inappropriate.[36] All studies reported multiple outcome measures, mostly with unadjusted *p* values. Many of the outcomes used in some trials were not reported in others, which rendered pooling of studies difficult. None of the trials stated a priori the primary outcome or efficacy measure upon which the overall conclusion of the study would be based. Using endpoints in this manner is suitable for exploratory rather than definitive research.[37]

While the overall quality scores (according to the Jadad scoring system) were good, examination of some key methodological features of these studies is informative. Of the 15 trials, 13 stated that they were randomized, but only 3 described the method of randomization. It has been demonstrated empirically that inadequate allocation concealment can exaggerate the estimate of treatment effect by 41% and that when the concealment methods are unclear the estimate of effect is exaggerated, on average, by 30%.[38] Eleven of the 15 papers did not mention or describe withdrawals or dropouts (although this information was provided subsequently by the authors of 2 papers), and none stated a planned intention-to-treat analysis. This technique analyzes patients within the group to which they were originally randomly allocated and serves to preserve the powerful function of randomization. Overall, given some of the design and statistical issues, all trials in this review had some risk of bias.

These combined findings related to design, quality and reporting of trials studying interventions for the management of AAP suggest the need for an organized, methodical research agenda in endodontics. Future research should be designed to provide consistent definitions of disease entities and should clearly state appropriate eligibility criteria for

various types of trials. More consistent and clinically relevant outcome measures, with patients as the unit of analysis, are important if efficacy is to be compared among therapies. Rigorous design and reporting of randomized controlled trials, consistent with the CONSORT statement,[39] would provide consistency in the reporting of research results. Much of the pain research that has been published used continuous scales such as the 100-mm Visual Analog Scale (VAS) to measure pain. Use of binary or dichotomous outcomes (for example, proportion of patients who achieve 50% pain relief or total pain relief by a certain time point) would enable the output from meta-analyses to be more intuitively understandable. Such methods would also be more useful to clinicians, because they would allow calculation of the numbers needed to treat.[40] The number needed to treat can be applied to treatment efficacy, adverse events and other clinical endpoints, is easily understood by clinicians and has immediate relevance for clinical decision making.[41,42] For example, 30 patients would have to be treated with a steroid–antibiotic intracanal medicament to ensure that 1 patient had mild or no pain postoperatively. On the other hand, only 4 patients would have to be treated with a preoperative systemic NSAID in conjunction with a pulpectomy for the same result. Clearly, the latter is a more effective therapy.

In this review, comprehensive search methods were used to minimize bias. Potential sources of bias include publication bias (unpublished studies were not sought) and language bias. Resources did not permit the costly translation of studies published in languages other than English or French. However, a recent study of a number of disease areas has shown that language-restricted and language-inclusive meta-analyses do not differ with respect to the estimate of benefit of an intervention.[43]

Now that the evidence on the emergency management of AAP has been assembled and synthesized, it is apparent that more research is needed in several areas, particularly relating to the most appropriate and effective drugs, routes, dosages and timing of analgesics and anti-inflammatory drugs. In planning these trials, appropriate inclusion criteria, attention to rigorous design and statistical issues, consistent use of validated measurement tools and choice of clinically relevant primary outcome measures are essential.

Recommendations for Practice

On the basis of the evidence gathered in this analysis, and within the study limitations, the following recommendations are made for adult patients with AAP (to be applied in conjunction with endodontic therapy). The strength of each recommendation has been graded according to the system of the U.S. Agency for Health Care Policy and Research[44] and the initial grading system of Sackett,[45] as outlined in Appendix 3.

- There is good evidence to support the use of NSAIDs for pain relief and pain control (grade A), especially when given immediately preoperatively (grade A).
- The use of antibiotics in the management of AAP is not recommended (grade B).
- There is some evidence to support the use of an NSAID solution as an intracanal medicament (grade B).
- Trephination through bone may be useful when done in the periapical region (grade B), but entry through the attached gingiva is not recommended (grade B).
- There is weak evidence to support the use of steroidal anti-inflammatory drugs (grade C) for pain management. ◆

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Appendix 1 Search strategy based on Medical Subject Headings (MeSH) for nonsteroidal anti-inflammatory drugs[a]

Steps	Medical Subject Headings	No. of citations
1	toothache/	1,306
2	pulpitis/	1,501
3	pulpitis. mp. (mp = title, abstract, registry number word, MeSH heading)	1,582
4	toothache.mp. (mp = title, abstract, registry number word, MeSH heading)	1,396
5	1 or 2 or 3 or 4	2,855
6	Periapical periodontitis/	629
7	5 or 6	3,405
8	exp Anti-inflammatory agents, non-steroidal/	90,129
9	7 and 8	108
10	Limit 9 to human	90
11	Limit 10 to (clinical trial or clinical trial, phase i or clinical trial, phase ii or clinical trial, phase iii or clinical trial, phase iv or consensus development conference or consensus development conference, nih or controlled clinical trial or meta analysis or multicenter study or practice guideline or randomized controlled trial)	27
12	Limit 11 to English language	16
13	exp treatment outcome/	114,518
14	exp "signs and symptoms"/	622,459
15	13 or 14	726,437
16	12 and 15	16
17	From 12 keep 1–16	16

exp = explode (MEDLINE abbreviation; designates a method whereby a subject heading is used as an umbrella term to capture more specific headings on the same subject).

[a]*The same strategy was used for all interventions, with appropriate key words used in step 8.*

Appendix 2 Studies excluded from analysis

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Appendix 3 Grading of evidence[44,45]

Level or grade[a]	Definition
Evidence	
Ia	Evidence obtained from meta-analysis of randomized controlled trials
Ib	Evidence obtained from at least one randomized controlled trial
IIa	Evidence obtained from at least one well-designed controlled study without randomization[b]
IIb	Evidence obtained from at least one other type of well-designed quasi-experimental study
III	Evidence obtained from well-designed nonexperimental descriptive studies, such as comparative studies, correlation studies and case studies
IV	Evidence obtained from expert committee reports or opinions and/or clinical experiences of respected authorities
Recommendations	
A	Based on at least one randomized controlled trial as part of a body of literature of overall good quality and consistency addressing the specific recommendation (evidence levels Ia, Ib)
B	Based on well-conducted clinical studies but no randomized clinical trials on the topic of the recommendation (evidence levels IIa, IIb, III); alternatively, small randomized trials with uncertain results (and moderate to high risk of error)
C	Based on evidence obtained from expert committee reports or opinions and/or clinical experiences of respected authorities; absence of directly applicable clinical studies of good quality (evidence level IV)

[a]*"Level" applies to categories of evidence; "grade" applies to categories of recommendations.*
[b]*Randomized controlled trials are considered to represent level IIa evidence if method of randomization is not clear.*