

The Use of Antibiotics to Prevent Flare-up after endodontic treatment of asymptomatic teeth with pulpal necrosis and periapical pathosis: an evidence-based literature study

Chow AD, Ho J, Maggiras J, Robertson S, Tang S, Walton P

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1.0 Background and Purpose

The use of prophylactic antibiotics in endodontic dentistry has been guided by the recommendations set forth by the American Heart Association (AHA). In general, the use of prophylaxis is indicated for immunosuppressed patients or individuals susceptible to cardiac infection such as endocarditis (Mata et al., 1985). In effect, this recommendation of antibiotic prophylaxis is meant to prevent the onset of dental infection that might spread systemically.

Research has also been conducted concerning the efficacy of antibiotics in treating asymptomatic teeth with pulpal necrosis and periapical pathosis (Abbott et al., 1988). While the use of systematic antibiotics alone to treat periapical abscess has been suggested ineffective (Grad, 1997), the use of antibiotics to prevent infection related post-operative pain and swelling is still contentious. Flare-up is a term commonly used to describe the characteristic symptoms of pain and swelling that may arise following endodontic treatment. However, amongst the dental community a great deal of variation exists in both the definition of flare-up and the best treatment solution to prevent its occurrence. Due to these differences and the lack of a definitive guideline, this report sets out to use an evidence-based approach to evaluate the available literature and answer the following question: should antibiotics be used to prevent flare-up after endodontic treatment of asymptomatic teeth with pulpal necrosis and periapical pathosis. This paper summarizes the strongest sources of evidence regarding this issue.

2.0 Target Population

This report aims to provide recommendations to patients suffering from periapical abscess or pulpal necrosis that requires endodontic intervention and to the dental practitioners that treat them. The literature suggests that these individuals are susceptible to possible flare-up following treatment. As suggested by Abbott et al. (1988), abscess and necrosis are common problems encountered by dental practitioners and it is estimated that 10% of a dentist's working time is used to treat such disease. Therefore, having a guideline regarding the use of antibiotics to prevent flare-up would benefit a significant number of patients.

3.0 Clinical Problem

While the main intention of endodontically treating periapical necrosis and abscess is the elimination and prevention of infection, reduction of flare-up is also important to facilitate recovery and minimize pain and swelling. The question remaining is whether the use of antibiotics can prevent the occurrence of such flare-up. Some investigators suggest that the failure to prescribe antibiotics to patients undergoing endodontic therapy not only increases potential flare-up, but might also lead to the exposure of potentially dangerous bacteria that are responsible for serious infections such as continuous bacteremia and septicemias, septic embolization, deep-space cellulitis, intracranial abscesses and Ludwig's angina (Abbott et al., 1988; Morse et al., 1987).

On the other hand, some investigators argue that there isn't enough evidence to advocate the use of antibiotics to prevent flare-up, and indiscriminate use of antibiotics to supplement treatment of dental infections can lead to serious consequences including allergic reactions, development of super-infections with resistant strains of bacteria, and side effects of the medications (Walton et al., 1993). Therefore, with such complications in mind, it is very important that the evidence supports the use of antibiotics in the prevention of flare-up.

4.0 Clinical Flexibility

This report deals with the evidence available concerning the efficacy of antibiotics in preventing flare-up after endodontic treatment of asymptomatic teeth with pulpal necrosis and periapical pathosis. If a guideline can be established regarding the use of antibiotics in the

prevention of flare-up, it may significantly limit the pain and suffering of patients as well as the dental chair time for unscheduled emergency appointments. In this report, we seek to establish an antibiotic guideline with regards for the prevention of flare-up following endodontic treatment of asymptomatic periapical pathosis and pulpal necrosis.

5.0 Structure of This Report

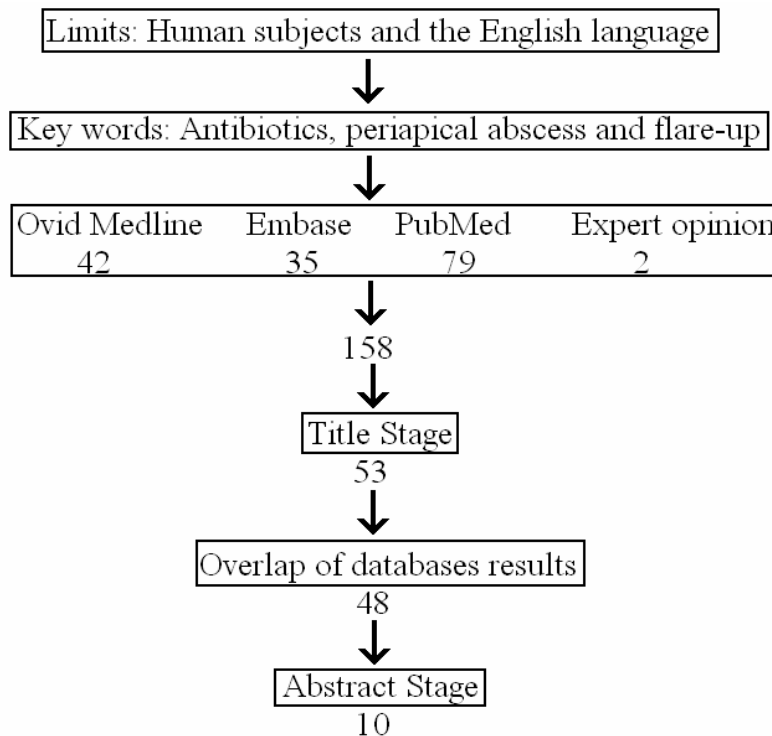
The findings of the current review are presented in this evidence-based report. The outline of the report is based on the template created by Leake et al. (1996). The template covers the following:

- Search strategy
- Inclusion criteria
- Summary of evidence
- Confounding Variables between studies
- Comparison of Outcomes
- Evidence-based recommendations
- Suggestions for further research

Evidence for the use of antibiotics in the prevention of flare-up

6.1 Search Strategy

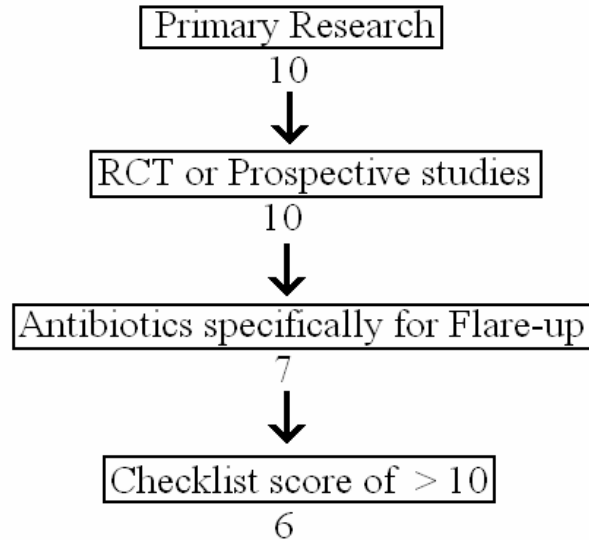
Ovid Medline, PubMed and Embase databases were combined with expert opinion to search the scientific evidence. The following strategy was used:



6.2 Inclusion/Exclusion Criteria

The articles subject to full text consideration were included if it met the following criteria. 1) The article was primary research/experiment. 2) The article examined the use of antibiotics for

flare-up, not prophylactic use to prevent heart disease or to treat a tooth abscess. 3) The study was of strong study design. 4) The study should score 10 or greater when evaluated using The University of Toronto Community dentistry checklist to assess evidence of efficacy of therapy or prevention developed by Leake (1997), and the CTFPHC system.



For all 10 articles evaluated, each of the six authors scored each study independently. Where scores differed by two or more points, the study was discussed and re-scored as a group. Only those studies that were re-scored as 10 or greater were included in this review.

7.0 Summary of Evidence

Pain and swelling are complications that are often encountered following endodontic treatment of asymptomatic teeth with pulpal necrosis and associated periapical radiolucent lesion (PN/PL) (Mata et al., 1985). In general, the term flare-up is used to describe moderate to severe pain and/or moderate to severe swelling that usually begins 12-48 hours after treatment, lasts at least 48 hours, and requires unscheduled emergency appointments (Abbott et al., 1988). Unfortunately, studies testing the efficacy of antibiotics to prevent pain and swelling often adopt different definitions of flare-up that ultimately render cross study comparisons difficult. Comparison of research evidence is also problematic due to differences between studies with respect to patient population, surgical procedures, post-operative analgesic use, and data collection. Moreover, the studies under examination use patient reports and questionnaires to obtain data on postoperative pain and swelling. Pain is a subjective perception that is difficult to quantify let alone compare between different individuals and as such is a problematic marker for detecting flare-up.

Mata et al. (1985) suggests that many factors may be etiologically involved in the production of pain and swelling following endodontic therapy. For instance, entrance of oxygen into the root canal during access may induce facultative aerobic bacteria to proliferate and produce inflammatory agents. Instrumentation and the air syringe can force bacteria into the canal and perhaps through the apical foramen. The use of local anesthetic or instrumentation might act as local irritants that cause an inflammatory response. Thus, there are many possible factors that might contribute to a flare-up. Regardless, the efficacious use of antibiotics necessitates bacterial involvement in the flare-up mechanism, otherwise antibiotic treatment is unwarranted and unjustified.

7.1 Role of antibiotics in preventing dental infection

Prevention of infection using antibiotics is established on the principles set forth by the work of Burke and Miles (Pickenpaugh et al., 2001). Antibiotics need to be in the tissue or wound site when it is seeded with bacteria in order to be effective. In animal models, delays of antibiotic administration by 3 to 4 hours resulted in infections indistinguishable to those in control animals. Thus, factors such as time of administration, dosage concentration, drug distribution and tissue penetration that affect the delivery of antibiotics to the site of infection are important in determining the efficacy of antibiotic treatment in preventing infection associated flare-up.

Ideally, the bacterial source would be known permitting the selection of the appropriate antibiotic to prevent infection. Endodontic related infections often consist of bacterial species that co-exist in a mixed synergistic relationship (Morse et al., 1990). In this way, it is possible to clear infection by eliminating penicillin sensitive species and indirectly reducing the pathogenicity of gram-negative species such as *Bacteroides* that depend on gram-positive bacteria for nutrients.

However, Pickenpaugh et al. (2001) state that “the difference between the experimental lesion of Burke and Miles, a freshly seeded bacterial wound, and the endodontic lesion is that the lesion of endodontic origin is long-standing in nature...[and]...therefore immunological factors of a pre-existing, chronic lesion may also be involved in a flare-up.” In this way, a flare-up may be the manifestation of multifactorial mechanisms, of which, antibiotics may only be partially effective in preventing.

7.2 Evidence in support of the use of antibiotics in preventing flare-up

Research supporting the use of antibiotics in preventing flare-up following endodontic treatment of PN/PL has come from investigators of Temple University School of Dentistry. Mata et al. (1985) used a randomized controlled trial to test the incidence of flare-up between patients receiving either penicillin V or a placebo control. The antibiotic dosage schedule was 250mg tablets of penicillin V every 6 hours for the first 24 hours followed by 1 tablet every 6 hours until all pills were gone. Flare up was defined as pain and/or swelling that necessitated an unscheduled emergency visit. After standard endodontic therapy was performed patients were asked to complete a pain and swelling questionnaire for 2 days. It was found that the incidence of flare up was 6% in the penicillin group and 24% in the control group.

In subsequent follow-up studies this research team defined flare-up as swelling and pain combined or swelling alone that necessitate unscheduled emergency appointments. However, the use of placebo controls were not deemed ethical, and the placebo control group from Mata et al. (1985) were used instead. Morse et al. (1987) randomly assigned patients to three treatment groups. Group A received 2g of Penicillin V one half hour before beginning of the treatment and an additional 1g 6 hours later, group B received 1g erythromycin stearate one half hour before beginning of the treatment and an additional 500mg 6hrs later and group C were given 1g erythromycin base one half hour before beginning of the treatment and an additional 500mg 6hrs later. No flare-up difference was found between the three groups and the overall incidence was 2.2%. Abbott et al. (1988) used the same treatment groups and found an overall flare-up incidence of 2.6%. Morse et al. (1990) compared flare up rate between patients given 1g of cefadroxil (a long acting cephalosporin) one half hour before beginning of the treatment and a placebo pill 6 hours later and 1g erythromycin stearate or base one half hour before beginning of the treatment and an additional 500mg 6hrs later. Once again there was no difference in flare-up incidence between the three groups and the overall incidence was 2%. However, when the antibiotic treatment groups from these three studies were compared to the control group from Mata et al., (1985) flare-up incidence was significantly lower in patients receiving antibiotics. According this body evidence, Abbott et al.

(1988) suggests “it is our opinion that the antibiotic regimens...should be a component of clinical endodontic therapy for quiescent PN/PL.”

7.3 Evidence against the use of antibiotics in preventing flare-up

In a randomized double blind study, Walton et al. (1993) compared the incidence of flare-up between patients receiving either 2g of Penicillin V at the beginning of the appointment and an additional 1g 6 hours later, an inert placebo control or no medication at all. Flare up was defined as severe pain and/or swelling requiring an unscheduled visit. Using a visual pain analog and swelling questionnaire, symptoms associated with flare-up were self evaluated and reported by patients at 4, 8, 12, 24, 48 hours post treatment. They found no difference in the incidence of flare-up between the different treatment groups and the overall rate of flare-up was under 2%. However, our calculations show that the sample size used by Walton et al. (1993) lacked the power needed to find a significant difference (power = 0.33; estimation of power was performed using DSTPLAN by B.W. Brown et al., 2000).

Pickenpaugh et al. (2001) gave patients either a 3g dose of Amoxicillin one hour before treatment or an inert placebo. Flare-up was defined as moderate-to-severe postoperative pain or moderate to severe swelling that began 12 to 48 hours after treatment and lasted at least 48 hours. The incident of flare-up was 6% in the amoxicillin group and 4% in the placebo group but this result was not statistically significant. Pickenpaugh et al. (2001) claim that their findings “disagree with the work of Morse and co authors.” Unfortunately, the study lacked adequate power (power = 0.08; estimation of power was performed using DSTPLAN by B.W. Brown et al., 2000) to make such claims definite.

8.0 Confounding variables between studies

8.1 Definition of flare-up

Utilization of different definitions of flare-up by different studies renders it difficult to compare results concerning the efficacy of antibiotics at reducing flare-up. For instance, Pickenpaugh et al. (2001) defined flare-up as moderate-to-severe postoperative pain or moderate to severe swelling that began 12 to 48 hours after treatment and lasted at least 48 hours. In essence, a flare-up could consist of pain alone in the absence of swelling or vice versa, but the symptom needed to persist for at least two days. Walton et al. (1993) chose flare-up to describe severe pain and/or swelling requiring an unscheduled visit. In this case, an unscheduled visit was necessary for a flare-up occurrence but the duration of the pain or swelling was not considered.

Perhaps most problematic is that the Temple University research team uses the control group from Mata et al. (1985) which uses pain and/or swelling that necessitated an unscheduled emergency visit as the definition of flare-up, whereas their subsequent studies adopted swelling and pain combined or swelling alone that necessitate unscheduled emergency appointments to define a flare-up. In their first definition, swelling is sufficient but not necessary for a flare-up but their latter definition requires the presence the swelling. It is our opinion that the placebo group from Mata et al. (1985) is not an appropriate control for Abbott et al. (1988), Morse et al. (1987) and Morse et al. (1990).

8.2 Irrigation concentrations

The studies under examination used different concentrations of sodium hypochlorite to irrigate the canal systems of teeth with PN/PL. Walton et al. (1993) and Pickenpaugh et al. (2001) irrigated with 2.5% and 2.62% sodium hypochlorite respectively. Mata et al. (1985) irrigated with concentrations ranging from 0.5-2.5%, Abbott et al. (1988) used 0.5%, and Morse et al. (1987) and

Morse et al. (1990) did not disclose the sodium hypochlorite concentration used. This lack of uniformity has several implications.

First, Carson et al. (2005) has shown that increasing concentrations of sodium hypochlorite is accompanied by increasing antimicrobial effectiveness *in vitro*. Second, increasing concentrations of sodium hypochlorite does not damage mineral content of root canal dentin (Ari et al., 2005), therefore there is no evidence contraindicating the use of higher concentrations. Thus, it is possible that patients in Mata et al. (1985) that received irrigation with low concentrations of sodium hypochlorite failed to obtain adequate antimicrobial action, and those patients subsequently given penicillin V were then able to eliminate remaining bacteria, whereas those given the placebo had no further protection against infection and flare-up. Interestingly, the control groups from the Walton et al. (1993) and Pickenpaugh et al. (2001) studies were irrigated with 2.5% and 2.62% sodium hypochlorite respectively, and the corresponding incidence of flare-up was low. Hence, it might be that variation in irrigant concentration is responsible for differences in the incidence of flare-up between studies.

8.3 Use of Analgesics

Since all definitions of flare-up are dependent on pain and swelling, the postoperative use of analgesics by patients make it difficult to standardize flare-up. Some patients may have controlled pain and swelling by using analgesics while others choose to make an emergency visit. Pickenpaugh et al. (2001) gave patients' ibuprofen or codeine (tylenol #3) to use as needed for pain and swelling relief. However, ibuprofen is both an analgesic and an anti-inflammatory agent, whereas tylenol #3 is purely an analgesic. This difference in therapeutic effect is important to note.

Mata et al. (1985) did not disclose if patients were permitted to use analgesics. Yet, in subsequent studies by the team at Temple University, patients were given ibuprofen, codeine (tylenol #3), diflunisal, or empirin. Information concerning which patients used which analgesic is not revealed in Morse et al. (1987, 1990) or Abbott et al. (1988). If the placebo control group in Mata et al. (1985) were not permitted to use analgesics, it would be impossible to use this population to compare against patients that were allowed to control pain and swelling with analgesics as was the case in Morse et al. (1987, 1990) and Abbott et al. (1988).

8.4 Problems associated with patient self-report of pain

The International Association for the Study of Pain defines pain as “an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage.” It is well known that an individual's tolerance and reaction to pain differs greatly from one person to the next (Marieb, 2001). This inherent difference between patients makes it difficult to standardize a flare-up event.

8.5 Duration of flare-up assessment

The studies under review also assess pain for different amounts of time. Using patient evaluated questionnaires, Mata et al. (1985) followed the development of pain in patients for 2 days, but in subsequent studies the Temple University group did not disclose how long patient pain was monitored. Walton et al. (1993) instructed patients to assess pain using a questionnaire at strict time intervals of 4, 8, 12, 24, 48 hours. In a slightly different manner, Pickenpaugh et al. (2001) instructed patients to keep a diary of pain assessed before going to bed on the day of treatment, then on arising and before bedtime each for 5 days.

There are several problems associated with these schedules of pain assessment. First, according to Pickenpaugh et al. (2001) an important feature of a flare-up is that its onset usually occurs 12-48 hours following treatment and lasts at least 48 hours. If in fact this is the case, the

studies of Mata et al. (1985) and Walton et al. (1993) do not adequately monitor pain development for long enough time periods. Second, reporting pain at predetermined intervals following the completion of endodontic treatment, makes it possible to standardize pain progression and development. Unfortunately, not all the studies did this. Third, by giving patients the opportunity to appraise their pain at the moment of the actual experience as opposed to waiting until the next assessment interval, patients may be able to more accurately report their pain state. Thus, it is difficult to compare the pain assessment data collected from different studies.

8.6 Adjusting occlusion

Occlusion following temporary filling placement were not adjusted in Pickenpaugh et al. (2001) and Walton et al. (1993), but were in Morse et al. (1987, 1990) and Abbott et al. (1988). It is not stated in Mata et al. (1985) if occlusion was adjusted following the commencement of treatment and the dismissal of the patient following the appointment. However, a high restoration may actually serve as a source of irritation and pain. Considering that all patients had periapical pathosis, it is reasonable to assume that apically directed forces occurring during occlusion could be important in the production of pain and swelling. Thus, in studies in which occlusion was not adjusted it is impossible to determine if flare-up is due solely to infection or local irritation due to excessive premature occlusal contacts.

8.7 Use of ZOE

Zinc oxide eugenol (ZOE) is used in dentistry as a temporary cement that has both palliative and antibacterial properties. ZOE was used as the temporary filling material in Mata et al. (1985), Morse et al. (1987, 1990) and Abbott et al. (1988). The temporary filling material used in Pickenpaugh et al. (2001) and Walton et al. (1993) is not stated and if the material used lacked these palliative and antibacterial properties it would obviously impact on the postoperative pain and likelihood of infection.

8.8 Clinic patients vs private-practice patients

In an attempt to offer an explanation for the high incidence of flare-up in the placebo control group, Mata et al. (1985) state that “private-practice patients might be more inclined to come in for unscheduled appointments...[and]...clinic patients tend to complain less than private patients.” Certainly, differences between clinic and private-practice patients exist and perhaps the results from the studies under review reflect this, rather than or as well as, real differences in flare-up incidence. Pickenpaugh et al. (2001) and Walton et al. (1993) used clinic patients in their studies and both found low incidence of flare-up in both controls and in the antibiotic group. Conversely, Mata et al. (1985) used private-practice patients and found a high incidence of flare-up in control patients.

Evidence-Based Recommendations

At present, inconclusive evidence exists making a concrete recommendation concerning the use of antibiotics to prevent flare-up after endodontic treatment of asymptomatic teeth with pulpal necrosis and periapical pathosis impossible. Research showing the efficacy of antibiotics in preventing flare-up is based solely on one control group that had an uncharacteristically high flare-up incidence. Studies showing the inefficacy of antibiotics are limited by a lack of power. However, we contend that the best evidence currently available suggests that the use of antibiotics is not warranted.

Need for Further Research

Future research should be aimed at addressing the weaknesses and confounding variables of the existing evidence as discussed in this review paper. Specifically, standardization of the definition of flare-up must be established and implemented in future research paradigms. Uniform concentrations of irrigant should be used to distinguish the role of antibiotics from intracanal disinfectant in reducing rates of flare-up. Lastly, standardization of analgesic use needs to be established in order to accurately categorize and detect true cases of flare-up.

TABLE 1: The Use of Antibiotics to Prevent Flare-up

Study	Flare-up definition	Population	Treatment	Irrigation	Analgesic	Duration of flare-up assessment	Flare-up incidence
Mata et al., (1985)	Pain and/or swelling that necessitated an unscheduled emergency visit	-Private practice patients -necrotic pulps diagnosed via hot and cold thermal tests and the electric pulp test and asymptomatic associated periapical radiolucencies	<u>GROUP A (n=50)</u> : two 250mg tablets of penicillin V every 6 hours for the first 24 hours followed by 1 tablet every 6 hours until all pills were gone <u>GROUP B (n=50)</u> : same but placebo pill was used	Irrigation with 0.5% - 2.5% sodium hypochlorite	Doesn't say	2 days after end of appointment -patient evaluated and reported -pain analog and swelling scale	6% flare-up in penicillin group 24% in the control group
Morse et al., (1987)	Swelling and pain combined or swelling alone that necessitate unscheduled emergency appointments	-Private practice patients -Ages: 12-74yrs -169 females and 146 men -Diagnosed with asymptomatic teeth with pulp necrosis and periapical radiolucent lesion but not stated how diagnosed	<u>GROUP A (n=105)</u> : oral 2g of Penicillin V ½ hour before beginning of the treatment and an additional 1g 6 hours later <u>GROUP B (n=?)</u> : 1g erythromycin stearate and an additional 500mg 6 hours later <u>GROUP C (n=?)</u> : 1g erythromycin base and an additional 500mg 6 hours later <u>PLACEBO</u> from Mata -Group B +C=210	Irrigation with unknown sodium hypochlorite concentrations	YES as needed	Unknown Might be 24 hours later and 1 week later -patient evaluated and reported -pain analog and swelling scale	No difference b/w antibiotics 2.2% flare-up with antibiotics Mata's control had 24%
Abbott et al., (1988)	Swelling and pain combined or swelling alone that necessitate unscheduled emergency appointments	-Clinic patients -Ages: 18-68yrs -104 females and 91 men -Diagnosed with asymptomatic teeth with pulp necrosis and periapical radiolucent lesion but not stated how diagnosed	<u>GROUP A (n=65)</u> : oral 2g of Penicillin V ½ hour before beginning of the treatment and an additional 1g 6 hours later <u>GROUP B (n=65)</u> : 1g erythromycin stearate and an additional 500mg 6 hours later <u>GROUP C (n=65)</u> : 1g erythromycin base and an additional 500mg 6 hours later <u>PLACEBO</u> from Mata et al. (1985)	Irrigation with 0.5% sodium hypochlorite	YES as needed	Unknown Might be 24 hours later and 1 week later -patient evaluated and reported -pain analog and swelling scale	No difference between antibiotics 2.6% Flare-up with antibiotics Mata's control had 24%

Morse et al., (1990)	Swelling and pain combined or swelling alone that necessitate unscheduled emergency appointments	-Private practice patients -Ages: 10-78yrs -99 females and 101 men -Diagnosed with asymptomatic teeth with pulp necrosis and periapical radiolucent lesion but not stated how diagnosed	<u>GROUP A (n=100)</u> : oral 1g of cefadroxil ½ hour before beginning of the treatment and a placebo pill 6 hours later, told it was antibiotic <u>GROUP B</u> : 1g erythromycin stearate and an additional 500mg 6 hours later <u>GROUP C</u> : 1g erythromycin base and an additional 500mg 6 hours later <u>PLACEBO</u> from Mata -Group B +C=100	Irrigation with unknown sodium hypochlorite concentrations	YES as needed	Unknown Might be 24 hours later and 1 week later -patient evaluated and reported -pain analog and swelling scale	No difference between antibiotics 2% flare-up w/ antibiotics Mata's control had 24%
Walton et al., (1993)	Severe pain and/or swelling requiring an unscheduled visit	-Clinic patients -Ages: 17-78yrs -32 females and 48 men -Diagnosed with pulp necrosis and chronic asymptomatic apical periodontitis but not stated how diagnosed	<u>GROUP A (n=26)</u> : oral 2g of Penicillin V at beginning of the appointment and an additional 1g 6 hours after the appointment <u>GROUP B (n=24)</u> : inert placebo of same regime <u>GROUP C (n=30)</u> : no medication	Irrigation with 2.5% sodium hypochlorite	Doesn't say	-Assessed at 4,8,12,24,48 hours post treatment -patient evaluated and reported -visual pain analog and swelling scale	No differences between groups 1.25% flare-up with antibiotics 0% in control group
Pickenpaugh et al., (2001)	Moderate-to-severe postoperative pain or moderate to severe swelling that began 12 to 48 hours after treatment and lasted at least 48 hours	-Clinic patients -Diagnosed with asymptomatic, necrotic tooth needing endodontic therapy -Tooth needed to test negative on an electric pulp test and to ice -Needed a periapical radiolucency of at least 3X3 mm	- <u>GROUP A (n=34)</u> : oral 3g Amoxicillin (6capsules) one hour before treatment <u>GROUP B (n=36)</u> : inert placebo of same regime	Irrigation with 2.62% sodium hypochlorite	YES as needed	-Diary recorded before going to bed on the day of treatment, then on arising and before bedtime each for 5 days -patient evaluated and reported -pain, percussion pain, swelling and amount of medication recorded	No difference between groups 6% flare-up with amoxicillin 4% in placebo control group

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