Comparison of the Efficacy of Various Ibuprofen and Acetaminophen Regimens on the Treatment of Post-Endodontic Pain

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COMPARISON OF THE EFFICACY OF VARIOUS IBUPROFEN AND ACETAMINOPHEN REGIMENS ON THE TREATMENT OF POST-ENDODONTIC PAIN

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ABSTRACT
COMPARISON OF THE EFFICACY OF VARIOUS IBUPROFEN AND ACETAMINOPHEN REGIMENS ON THE TREATMENT OF POST-ENDODONTIC PAIN

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Introduction: The purpose of this study was to determine the efficacy of taking ibuprofen and acetaminophen at the same time versus alternating the same medications in patients with a diagnosis of symptomatic irreversible pulpitis.

Materials and Methods: Ten patients who presented for root canal therapy with a diagnosis of symptomatic irreversible pulpitis were included in this study. The patients were randomly assigned to 2 groups. Following root canal therapy, the patients in group A were instructed to take ibuprofen 600 mg and acetaminophen 1000 mg every six hours. Patients in group B were instructed to take ibuprofen 600 mg, wait three hours, take acetaminophen 1000 mg, wait three hours, and repeat the cycle. Patients evaluated their pain levels using a numeric rating scale (NRS) at 2, 4, 6, 8, 12, and 24 hours post-operatively.

Results: The average preoperative pain level was 4.0 ± 2.0 for group A and 4.4 ± 3.05 for group B. The pain levels for group A were 3.4 ± 2.61 at 2 hours, 2.8 ± 1.79 at 4 hours, 2.6 ± 1.52 at 6 hours, 3.0 ± 2.0 at 8 hours, 2.4 ± 2.61 at 12 hours, and 2.2 ± 2.68 at 24 hours. The pain levels for group B were 2.2 ± 0.84 at 2 hours, 2.0 ± 0.71 at 4 hours, 1.8 ± 0.84 at 6 hours, 2.0 ± 1.22 at 8 hours, 1.6 ± 0.55 at 12 hours, and 1.4 ± 0.55 at 24 hours.

Conclusions: The data shows a trend toward having no significant difference between the two test groups.

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Introduction

Many patients who are treated at endodontic practices report pain due to irreversible pulpitis. While root canal therapy aims to eliminate this pain, there can still be discomfort following the procedure. Numerous medications have been used to treat this post-endodontic pain including NSAIDs (i.e. ibuprofen), acetaminophen, steroids, prescription narcotics, and antibiotics. This study is a further investigation into how the timing of doses of two commonly used over-the-counter pain medications, ibuprofen and acetaminophen, might alleviate post-operative pain.

Pulpitis, as the name implies, is inflammation of the pulp due to caries or the restorative process, such as a deep restoration or a crown preparation. The process of pulpal inflammation has been described in detail (Kim, 1990). Trauma to the pulp causes the release of vascular mediators including histamine and serotonin. These mediators then cause an increase in vasodilation and vascular permeability, leading to an initial increase in pulpal blood flow followed by a decrease in blood flow. Also among the mediators released following noxious stimuli are prostaglandins. Prostaglandins, especially PGE_2, can cause hyperalgesia, vasodilation, and increased vascular permeability. Due to the pulp being a low compliance system, this immune response can lead to an increase in pulpal tissue pressure, hypoxia, and pulpal necrosis, all of which can produce significant pain. Root canal therapy aims to remove the pulp, thereby eliminating the source of pain. However, inflammatory mediators (i.e. prostaglandins) may still be present in the periapical tissues (Shimauchi et al., 1997).

Also, the root canal procedure itself can trigger production of prostaglandins due to the trauma of severing the pulp and the irritation of the PDL subsequent to establishing patency, cleaning, and shaping (Siqueira and Barnett, 2004). This inflammatory process in the periradicular areas of the tooth after treatment can produce post-operative pain.

One of the most commonly used pain medications is ibuprofen. A survey published by Mickel, et al. (2006) showed that endodontists recommend ibuprofen 600-800 mg significantly more than any other pain medication. Due to the mechanism of action, ibuprofen is able to treat both pain and inflammation at the site of injury. Ibuprofen is a non-steroidal anti-inflammatory drug (NSAID). This class of drugs, which includes aspirin, works by blocking the conversion of arachidonic acid to prostaglandins via the cyclooxygenase (COX) -1 and -2 pathways. By preventing the production of prostaglandins, inflammation can be reduced and pain managed. It has been shown in numerous studies that ibuprofen 400-800 mg is more effective than almost all other pain medications, including acetaminophen (APAP), narcotics, and combinations of narcotics and APAP (Winter et al., 1978; Cooper, 1984; Cooper et al., 1989; Barden et al., 2004; Derry et al., 2009; Hersh et al., 2011). The U.S. Food and Drug Administration (FDA) has set the maximum single dose of ibuprofen at 800 mg and the maximum daily dose at 3200 mg. The potential side effects of ibuprofen range from mild to severe and include nausea, gastrointestinal bleeding, diarrhea, constipation, headache, dizziness, rash, renal impairment, stroke and heart attack. These adverse reactions, however, are rare; the more serious cardiovascular risks are seen only in patients taking long-term high doses. Ibuprofen has also been shown to interfere with the antiplatelet activity of

aspirin. Because the prostaglandin pathway is blocked by ibuprofen, much of the arachidonic acid is converted through the still-viable lipoxygenase pathway into leukotrienes. Some leukotrienes are responsible for bronchoconstriction, which can lead to an asthma attack in asthmatic patients. For this reason, those with asthma should not take ibuprofen.

Acetaminophen is another commonly used over-the-counter pain medication. While the method of action is not fully understood, it is thought that it generally affects pain perception centrally rather than peripherally as ibuprofen and other NSAIDs do. Recent work has found that the metabolite AM404 is responsible for all or part of the analgesic effects of acetaminophen (Högestätt, 2005). There has also been speculation that acetaminophen has some capacity as a COX-2 inhibitor, but this may be limited at the site of inflammation (Hinz et al., 2008). The FDA recommends the maximum single dose be limited to 1000 mg and the daily dose to 4000 mg. At these levels, adverse effects are rare but can include nausea and other stomach issues. At higher doses, APAP can cause acute hepatotoxicity.

Recently, there has been more evidence supporting a combination of both ibuprofen and acetaminophen in the treatment of post-operative pain. A study by Menhinick et al. demonstrated that, following root canal therapy, a combination of ibuprofen 600 mg and APAP 1000 mg was more effective than ibuprofen 600 mg alone at treating post-operative pain (Menhinick et al, 2004). Mehlisch et al. (2010) found that a combination of ibuprofen 400 mg and APAP 1000mg relieved pain better that a

combination of ibuprofen 200 mg and APAP 500 mg, ibuprofen 400 mg alone, or APAP 1000 mg alone. The addition of acetaminophen to ibuprofen has an additive effect that can preclude the need for narcotic analgesics and thus avoiding the undesired side effects (Hargreaves et al., 2005).

Following root canal therapy, patients can experience post-endodontic pain. O'Keefe (1976) reported on the incidence and severity of post-endodontic pain. He found that 50.9% of patients reported no pain, 47.2% reported mild pain, and 1.8% reported moderate to severe pain. Included in this study were patients with all types of pulpal diagnoses, so the results cannot be extrapolated to calculate the incidence of pain only in patients with symptomatic irreversible pulpitis. One other significant finding from the study is that patients who reported moderate to severe pre-operative pain were five times more likely to experience moderate to severe post-operative pain than those patients who reported none to mild pre-operative pain.

While several studies as stated above have shown the efficacy of a combination of ibuprofen and acetaminophen, there has not been a study designed to determine if differing dosing regimens of these two medications offer better pain relief than others. One possibility when alternating the medications is that it will allow the maximum effect, which occurs soon after administration, of each drug to be offset. The peak effect of each medication will occur as the effect of the previous medication is diminishing (Figure 1). The other possibility is that the effects of either medication could wear off before the next dose of the other medication is to be taken (represented

by * in Figure 2). The same theories could hold true for taking the medications at the same time. The first possibility is that the additive effects of the medications could produce sufficient analgesia over a long enough period that the pain relief is always greater than the minimum concentrations needed to produce said relief (Figure 3). The second is that the medications, which are metabolized by different processes, could be degraded quickly enough that it results in pain relief declining below effective levels before the next scheduled dosage (represented by * in Figure 4).

The aim of this study will be to investigate whether there is a difference in the pain relief following root canal therapy on teeth exhibiting symptomatic irreversible pulpitis between administering ibuprofen 600 mg and APAP 1000 mg at the same time every six hours and alternating the same medications every three hours. The null hypothesis states that there will not be a difference in analgesic effect between administering ibuprofen 600 mg and APAP 1000 mg at the same time every six hours, and alternating these same medications every three hours. The alternative hypothesis is that either group will experience more profound pain relief than the other.

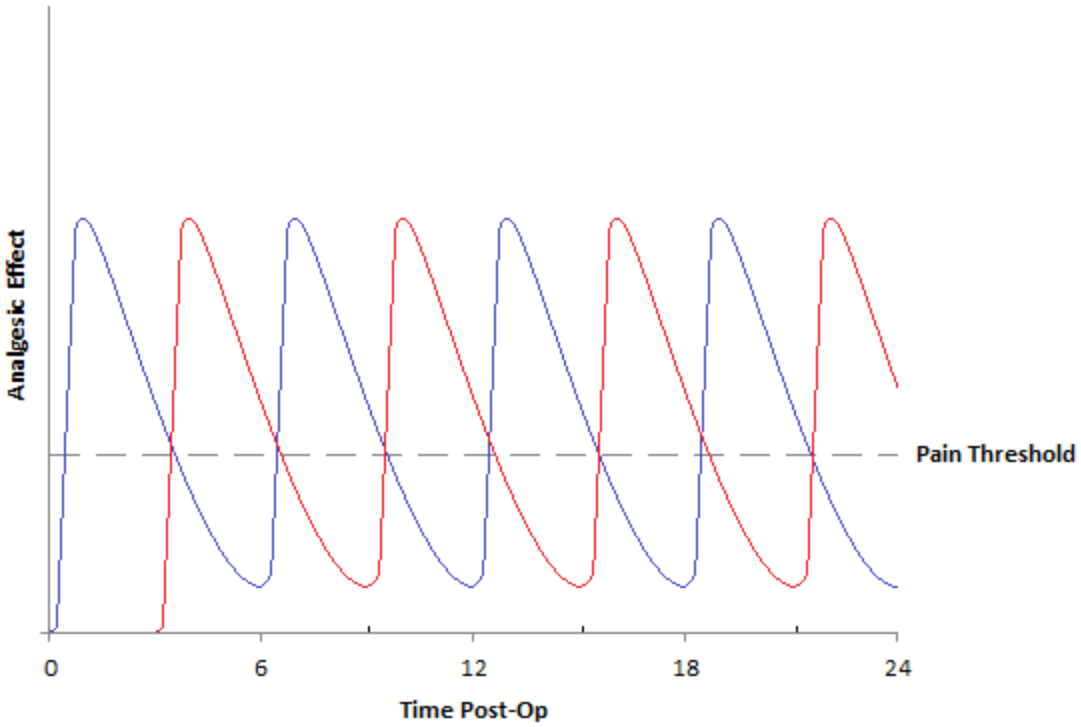

Figure 1. Proposed theory of the benefit of alternating medications. The effect of the second medication (red) begins just prior to the point at which the effect of the first medication (blue) is diminishing below the effective level.

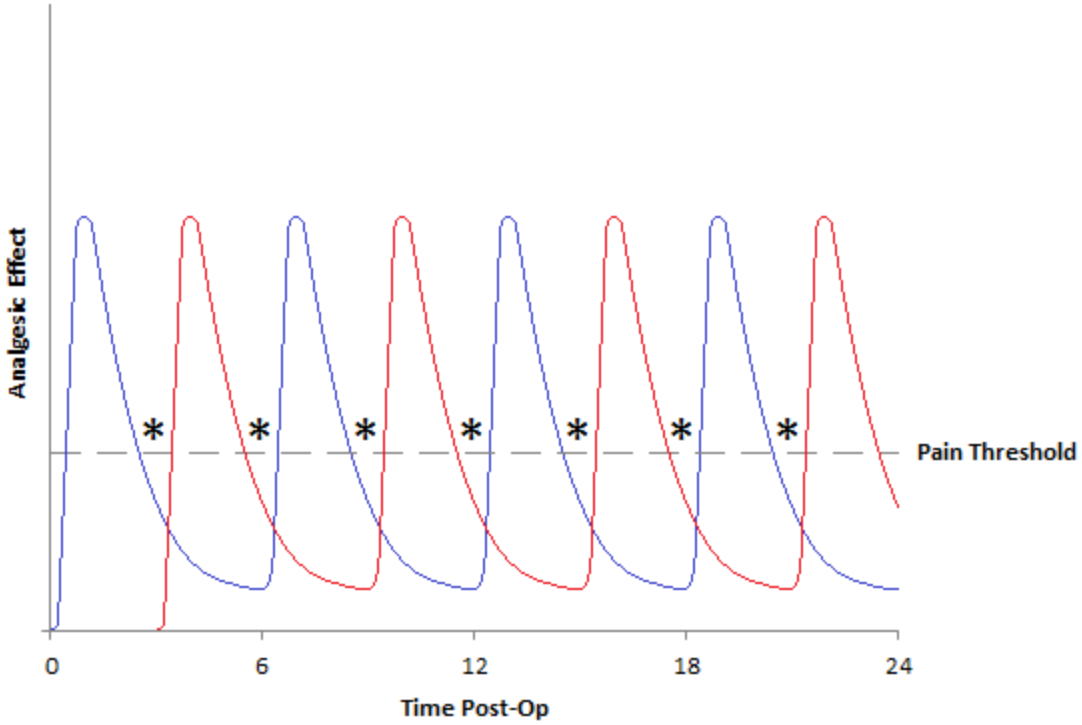

Figure 2. Proposed theory of the drawback of alternating medications. The effect of the first medication (blue) diminishes below the effective level before the effect of the second medication (red) can reach therapeutic doses (noted by *).

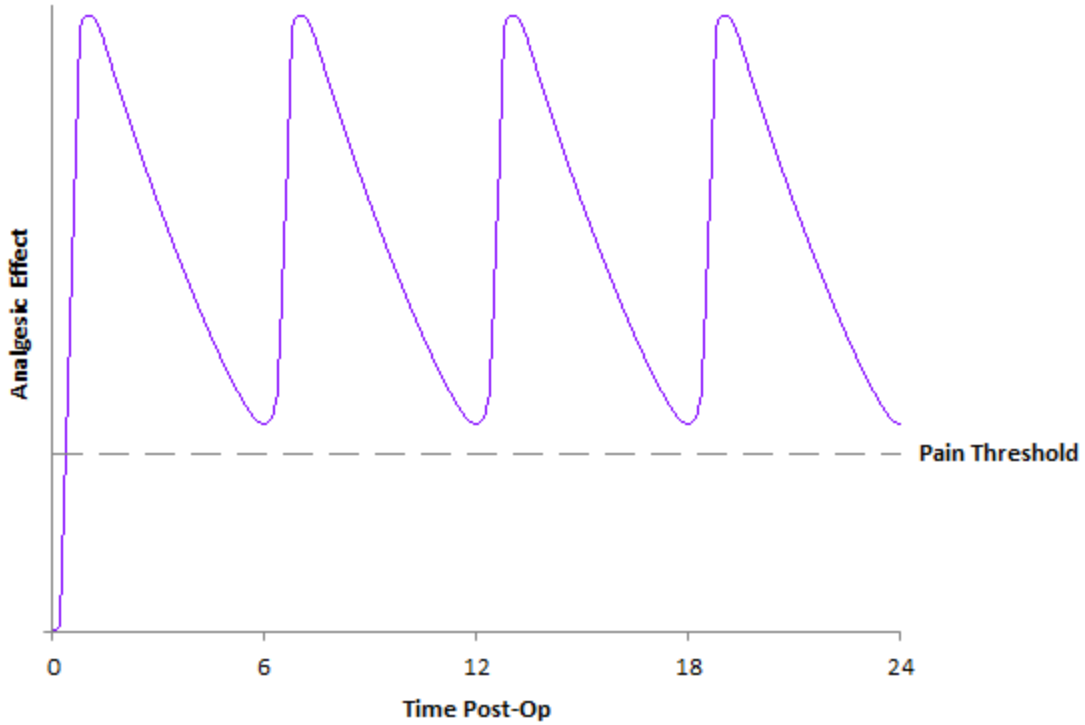

Figure 3. Proposed theory of the benefit of taking both medications at the same time. The purple line represents the additive effect of the medications. In this case, taking both medications at the same time provides enough analgesia over a sufficient amount of time to never drop below therapeutic levels.

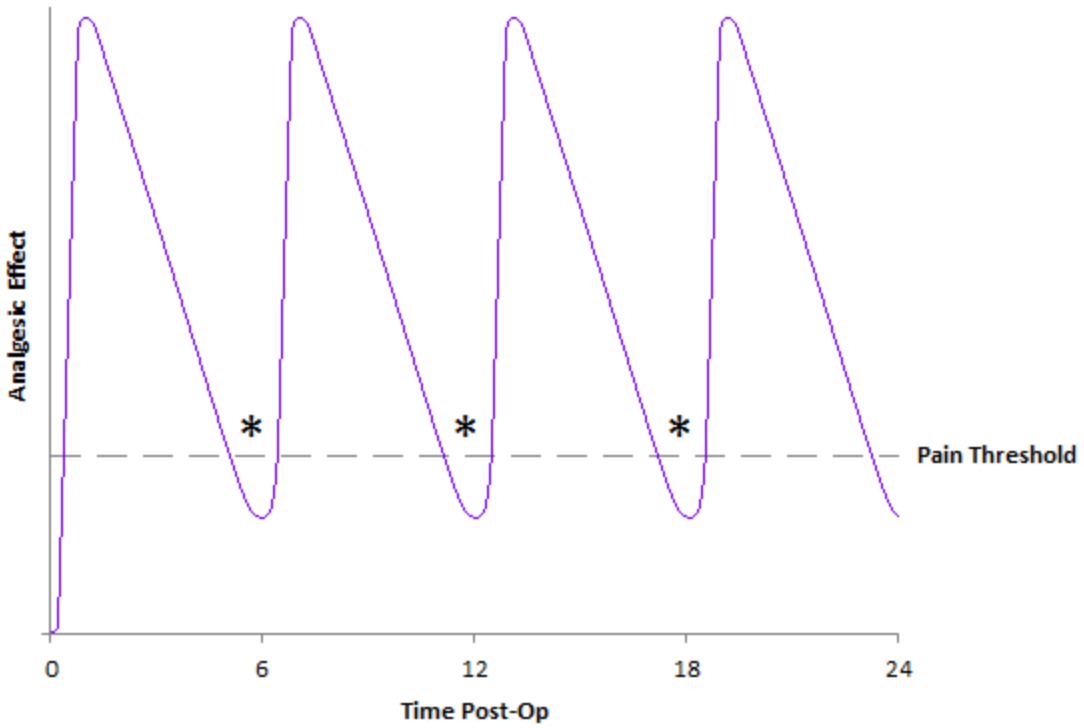

Figure 4. Proposed theory of the drawback of taking both medications at the same time. Although the additive effects of the medications (purple) produce a higher level of analgesia than either medication alone, the combined effects diminish before the next dose is taken (noted by *).

Materials and Methods

The protocol for this study was approved by the Marquette University Institutional Review Board (Protocol HR-2194). Ten adult patients participated in this study. All patients were determined to be in good health following a review of the health history and oral questioning. The following exclusion criteria were applied: age less than 18 years, pregnancy, ibuprofen or acetaminophen use within the last 12 hours, allergy to ibuprofen or acetaminophen, diagnosis of a bleeding disorder (i.e. hemophilia or Von Willebrand's disease), liver or kidney disease, peptic ulcer disease, long-term corticosteroid use, diagnosis of Inflammatory Bowel Disease (i.e. Ulcerative Colitis or Crohn's Disease). All patients gave written informed consent.

The patients in this study all had a diagnosis of symptomatic irreversible pulpitis. The diagnosis was determined by testing with Endo-Ice (Hygenic Corp, Akron, OH), an electric pulp tester (Analytic Technology Corp, Redmond, WA), and, as necessary, heat using gutta percha on a System B tip (SybronEndo, Orange, CA). If there were any indication of advanced pulpal pathosis with periapical involvement, such as a periradicular radiolucency or draining sinus tract, the patient was not included in the study. Patients rated their pre-operative pain levels using a numeric rating scale (NRS) on a scale from 1 (no pain) to 10 (severe pain) (Figure 5).

All endodontic procedures were performed by endodontic residents and completed in a single visit. Topical benzocaine (Topex; Sultan Healthcare, Ontario, Canada) was applied to the injection sites prior to anesthesia. All maxillary teeth were

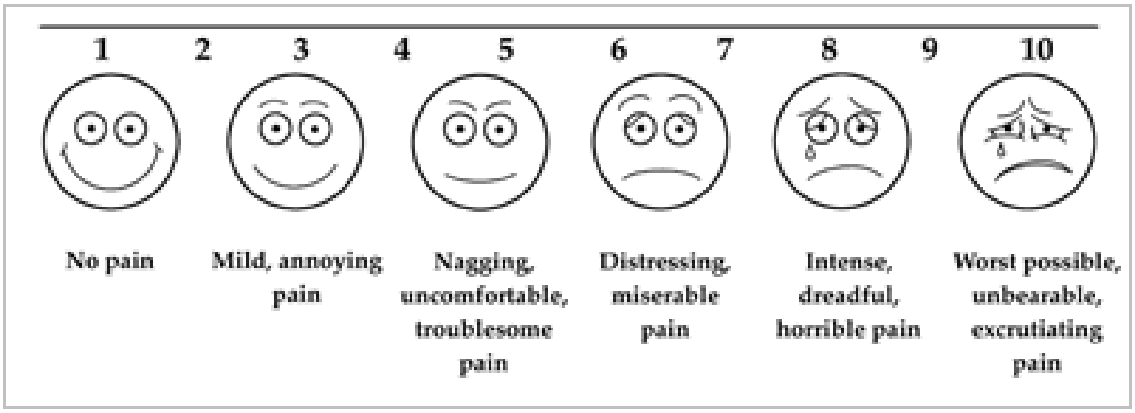

Figure 5. The numeric rating scale (NRS) used by patients to determine pain levels.

anesthetized using 68-132 mg of 4% articaine with 1:100,000 epinephrine (Septocaine; Septodont, Louisville, CO) by buccal and lingual infiltration. All mandibular teeth were anesthetized using 34-68 mg of 2% lidocaine with 1:100,000 epinephrine (Xylocaine; Dentsply, York, PA) by inferior alveolar nerve block and 34 mg of 4% articaine with 1:100,000 epinephrine by buccal infiltration. If necessary, 51-102 mg of 3% carbocaine without epinephrine (Mepivacaine; Carestream Health, Rochester, NY) was administered by inferior alveolar nerve block. Pulpal anesthesia was confirmed by no response to Endo-Ice or EPT. After successful anesthesia, a rubber dam was placed, and access into the pulp chamber was achieved. If purulence or lack of vital tissue was found in any canals at this time, the patient was excluded from the study. Working length was determined using a Root ZX II apex locator (J Morita Corp, Tokyo, Japan). Copious amounts of 5.25% NaOCl were used as irrigation, and Glyde (Dentsply-Tulsa Dental, Tulsa, OK) was used as a canal lubricant. Each canal was filed to a size 20/.02 hand file. The canals were then prepared using rotary instrumentation (RaCe and EndoSequence, Brasseler USA, Savannah, GA) in a modified crown-down technique. The final master apical file size was determined according the size and shape of the original canal. Radiographs with the master gutta percha cones in place were used to verify working length, and adjustments were made as needed. All canals were rinsed using aqueous 17% EDTA (Roydent, Johnson City, TN) and 5.25% NaOCl using a ProRinse side-port Luer-Lok needle (Dentsply-Tulsa Dental) and a 6 cc disposable plastic Luer-Lok syringe. The canals were then dried with paper points (EndoSequence, Brasseler USA). The master cones were coated with AH Plus sealer (Dentsply-Tulsa Dental). Obturation

was completed using warm vertical compaction by burning down to 3-6 mm from the apex using a System B and backfilling using an Obtura II or III Max (Obutra Spartan, Fenton, MI). The pulp chamber was temporized using sterile sponge or cotton pellet and either Cavit (3M ESPE AG, Seefeld, Germany) or Fuji Triage (GC America Inc, Alsip, IL).

Following treatment, the patients given two bottles of medications labeled A and B. Bottle A contained 12 liquigel capsules of ibuprofen 200 mg (PL Developments, Westbury, NY). Bottle B contained 8 capsules of quick release acetaminophen 500 mg (LNK International Inc, Seattle, WA). Patients were randomly assigned to one of two groups. Patients in group A were instructed to take three capsules (600 mg) of bottle A and two capsules (1000 mg) of bottle B every six hours. Patients in group B were instructed to take three capsules (600 mg) of bottle A, wait three hours, then take two capsules (1000 mg) of bottle B, wait three hours and repeat the cycle.

Patients were given an instruction sheet and an NRS and were instructed to record their pain levels at 2, 4, 6, 8, 12, and 24 hours post-operatively. If the study medications were not sufficient in relieving pain, the patients were instructed to call a pre-paid cell phone carried by the lead investigator (E.D.D.). Patients would then be prescribed tramadol and instructed to continue the study medications as needed. If the patient developed severe pain or swelling, he or she would be seen clinically and evaluated for the need for additional treatment and/or medications, including antibiotics. The patients were contacted the following day and their data recorded.

Results

Ten patients participated in the study with 5 patients in each group. The mean pain levels can be found in Table 1 and Figure 6. The patients in group A (mean age, 40.2; range, 25-62) consisted of 1 male and 4 females. The responses from the individual patients in group A can be seen in Figure 7. The patients in group B (mean age, 35.0; range, 26-51) consisted of 5 females. The responses from the individual patients in group B can be seen in Figure 8. The average preoperative pain for group A was 4.0 ± 2.0. The pain levels for group A were 3.4 ± 2.61 at 2 hours, 2.8 ± 1.79 at 4 hours, 2.6 ± 1.52 at 6 hours, 3.0 ± 2.0 at 8 hours, 2.4 ± 2.61 at 12 hours, and 2.2 ± 2.68 at 24 hours. The average preoperative pain for group B was 4.4 ± 3.05. The pain levels for group A were 2.2 ± 0.84 at 2 hours, 2.0 ± 0.71 at 4 hours, 1.8 ± 0.84 at 6 hours, 2.0 ± 1.22 at 8 hours, 1.6 ± 0.55 at 12 hours, and 1.4 ± 0.55 at 24 hours.

Time Post-Op (h)	Pain Level*	
	Group A	Group B
Pre-Op	4.0 ± 2.0	4.4 ± 3.0
2	3.4 ± 2.6	2.2 ± 0.8
4	2.8 ± 1.8	2.0 ± 0.7
6	2.6 ± 1.5	1.8 ± 0.8
8	3.0 ± 2.0	2.0 ± 1.2
12	2.4 ± 2.6	1.6 ± 0.5
24	2.2 ± 2.7	1.4 ± 0.5

* Mean ± Standard Deviation

Table 1. Average pain levels reported at each time interval per group.

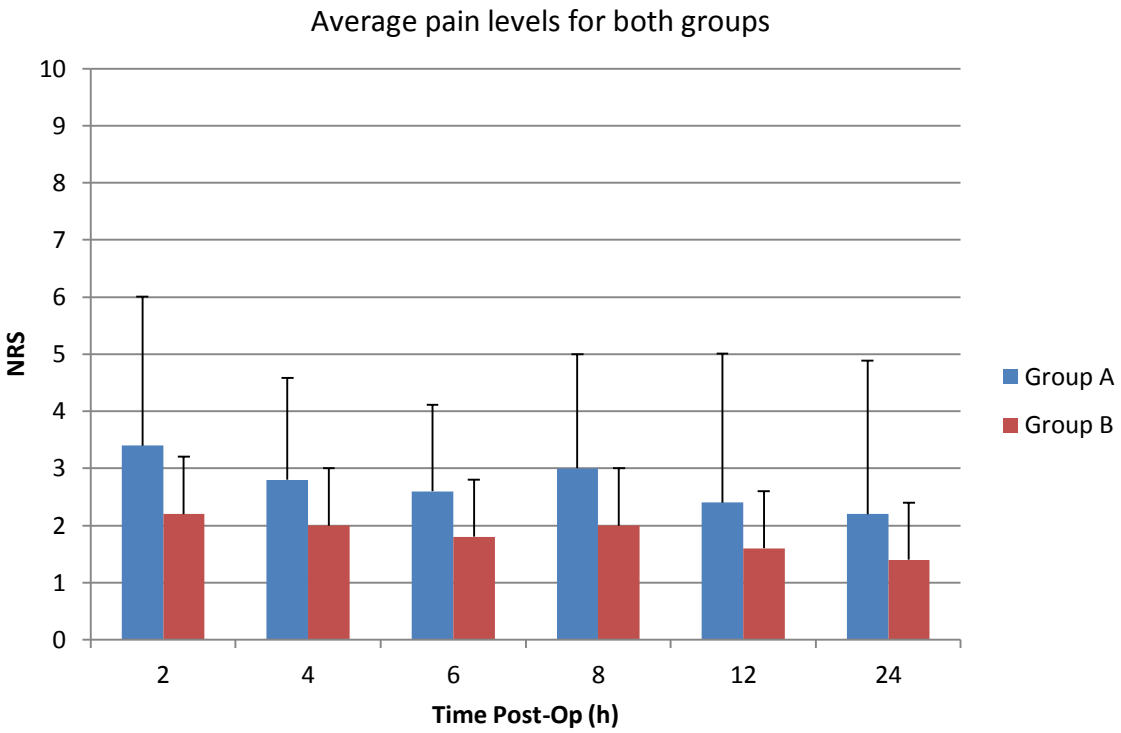

Figure 6. The mean pain levels and standard deviations reported for each group.

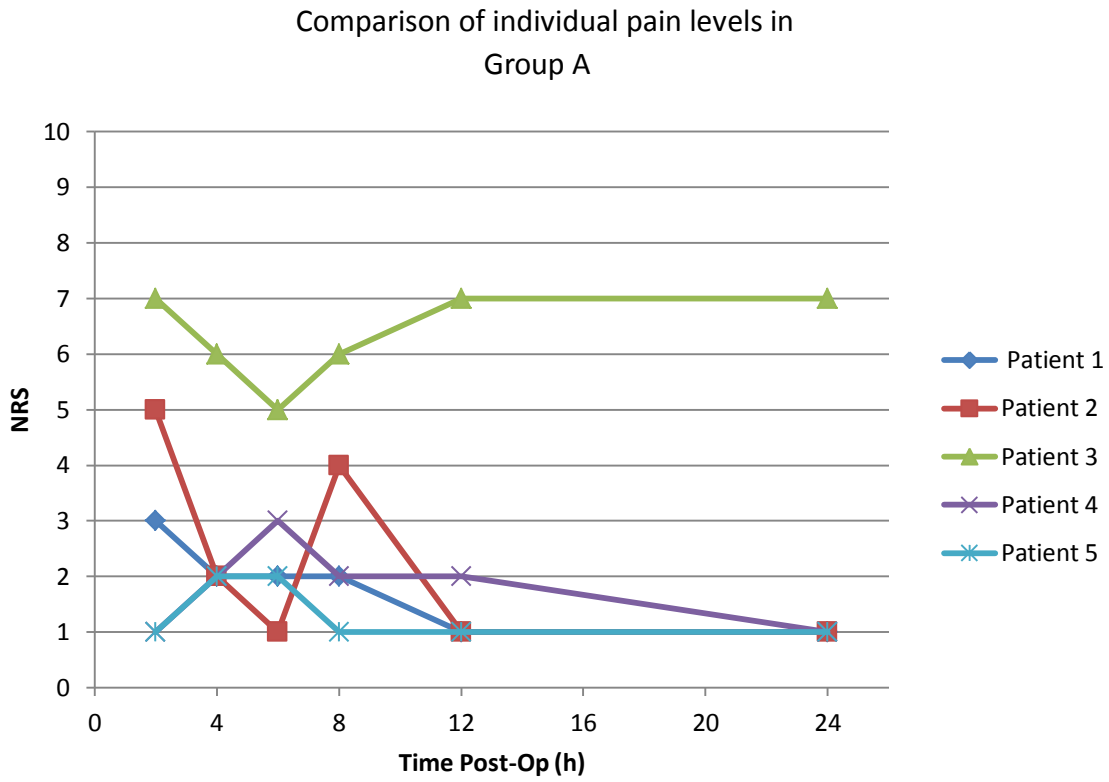

Figure 7. Responses from each individual patient in group A.

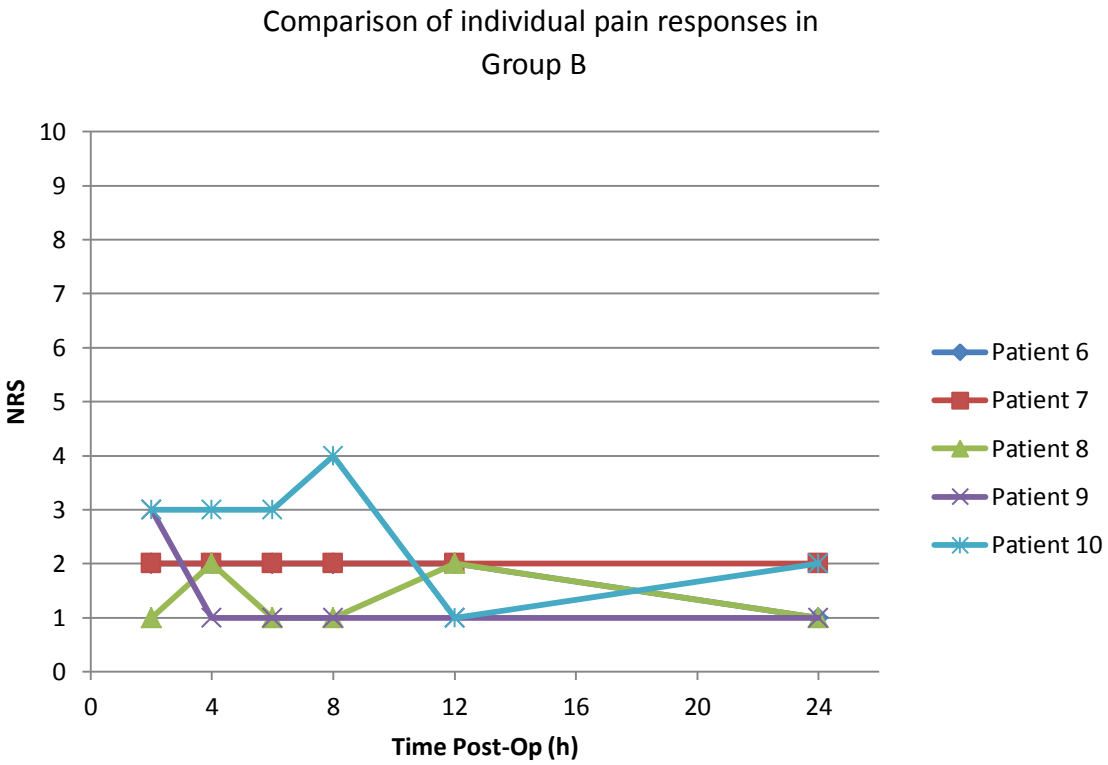

Figure 8. Responses from each individual patient in group B.

Discussion

The data exhibits a trend towards being not significantly different between the two treatment groups. While the data seems to conclude that patients in group B experienced greater pain relief than those in group A, it should be noted that the standard deviation for group A is much greater than that of group B. Because of the variability in the small sample size, it cannot be concluded that the difference will be significant. The larger standard deviation is likely due to one patient in group A who reported pain levels that were much greater than any other participant (Figure 6). It is possible that the patient reacted more severely to treatment than the other patients. This patient, however, did not feel the need to contact the investigator for prescription medication. Although using the NRS should normalize variances, patients perceive pain differently. While some patients may report a certain level of pain as 2, others may perceive that same pain as 4. This subjective variance may be negated with an increase in the number of participants. Additionally, it is not known how the slight difference in gender makeup between the two groups contributed to the findings.

It could be expected that if a difference were to exist, it would be recognizable at either the 4- or 6-hour response time. One explanation as to why no significant difference is seen between the two test groups is that the medications have a longer additive effect than 6 hours. This is supported by other research (Menhinick et al., 2004; Mehlisch et al., 2010). It is expected that the pain levels be low when alternating the medications as the peak effect of one drug is only 3 hours apart from the peak of

the drug. When taking both acetaminophen and ibuprofen at the same time, the peak effect could be much greater initially and the decrease in effect more gradual than taking either medication alone (Figure 3). In this way, the therapeutic levels may be maintained above the threshold at which the patient would feel pain during the entire 6 hours before the next dose.

It is difficult to separate the causes of pain in cases of irreversible pulpitis and necrosis. Necrotic teeth have a bacterial component that could have a significant impact on the amount of pain experienced following root canal therapy. This bacterial aspect adds an additional layer to the inflammatory reaction, one not mediated solely by inflammatory mediators but also by the immune system and its goal of eliminating the bacteria present. A recent study by Wells et al. (2011) showed that there was no difference in pain relief following root canal therapy on necrotic teeth between groups taking either ibuprofen 600 mg alone or a combination of ibuprofen 600 mg and APAP 1000 mg. This information can be compared with the results of the Menhinick et al. (2004) study to suggest that there may be a compounding factor in necrotic cases in relation to the cause of pain.

Many previous studies investigating pain medications evaluated pain after cleaning and shaping but before obturation (Torabinejad et al., 1994; Menhinick et al., 2004; Wells et al., 2010). Root canal therapy consists also of obturation which can be a source of post-operative pain (Harrison et al., 1983). This study was aiming to be more complete in terms of pain relief following a root canal since all treatment was

performed in a single visit. In recent years, a majority of endodontists have begun to perform single step non-surgical root canal therapy (Inamoto et al., 2002). There have also been several studies that investigated the pain following single- or multiple-step root canals (Roane et al., 1983; DiRenzo et al., 2002; ElMubarak et al., 2010; Wang et al, 2010). Most investigators found there was no difference between single and multiple visit non-surgical root canal therapy in terms of the level of pain experienced by the patient. Roane et al. determined that there was actually less pain following single-step endodontics when compared to two-step endodontics. Because there is relatively little difference in pain between single and multiple visit root canals, this study is applicable for most practitioners.

The duration of evaluation of pain in this study was 24 hours. While some studies have investigated duration of pain for longer (Wells et al., 2011), Harrison et al. (1983) found that the highest incidence and degree of pain following obturation was in the first 24 hours. While post-operative pain is not limited to only 24 hours, the level of pain should decrease significantly after the first day. To treat pain after this initial period, patients can be advised to continue medication for 2-3 days following the procedure (Hargreaves and Abbott, 2005).

Several recent studies have shown the efficacy of liquigel ibuprofen (Hersh et al, 2000; Olson et al, 2001; Doyle et al., 2002). Hersh et al. demonstrated that liquigel ibuprofen had a faster onset of pain relief and greater peak pain relief. The theory may also apply to quick release acetaminophen. These capsules are designed to break open

quickly in the stomach, allowing for faster delivery of the drug. While faster delivery leads to faster onset of pain relief, there have been no studies investigating whether the duration of pain relief is affected.

As the results of the study are showing a trend towards a non-significant difference, it would be reasonable to suggest that patients take both medications at the same time. This schedule would likely increase patient compliance and reduce post-operative complications. Patients are more likely to miss a dose if they need to remember to take one every three hours as opposed to every six hours. If a patient forgets to take the medication at a certain time, there could be an increase in the pain, which could lead a patient to schedule an emergency visit or request stronger (i.e. narcotic) pain medications.

Conclusion

The results of this study indicate that there is trend toward there being no difference in pain relief between taking ibuprofen 600 mg and acetaminophen 1000 mg together or alternating the same medications. Further studies with an increased number of subjects are needed to either validate or refute these findings.

Bibliography

Barden J, Edwards JE, McQuay HJ, Wiffen PJ, Moore RA. Relative efficacy of oral analgesics after third molar extraction. Br Dent J. 2004;197(7):407-11.

Cooper SA. Five studies on ibuprofen for postsurgical dental pain. Am J Med. 1984;77:70-7.

Cooper SA, Schachtel BP, Goldman E, Gelb S, Cohn P. Ibuprofen and acetaminophen in the relief of acute pain: a randomized, double-blind, placebo-controlled study. J Clin Pharmacol. 1989;29(11):1026-30.

Derry C, Derry S, Moore RA, McQuay HJ. Single dose oral ibuprofen for acute postoperative pain in adults. Cochrane Database Syst Rev. 2009;3:CD001548.

DiRenzo A, Gresla T, Johnson BR, Rogers M, Tucker D, BeGole EA. Postoperative pain after 1- and 2-visit root canal. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2002;93(5):605-10.

Doyle G, Jayawardena S, Ashraf E, Cooper SA. Efficacy and tolerability of nonprescription ibuprofen versus celecoxib for dental pain. 2002;42(8):912-9.

Hargreaves K, Abbott PV. Drugs for pain management in dentistry. Aust Dent J. 2005;50(4 Suppl 2):S14-22.

Harrison JW, Baumgartner JC, Svec TA. Incidence of pain associated with clinical factors during and after root canal therapy. Part 2. Postobturation pain. J Endod. 1983;9(10):434-8.

Hersh EV, Levin LM, Cooper SA, Doyle G, Waksman J, Wedell D, Hong D, Secreto SA. Ibuprofen liquigel for oral surgery pain. Clin Ther. 2000;22(11):1306-18.

Hersh EV, Kane WT, O'Neil MG, Kenna GA, Katz NP, Golubric S, Moore PA. Prescribing recommendations for the treatment of acute pain in dentistry. Compend Contin Educ Dent. 2011;32(3):22,24-30.

Hinz B, Cheremina O, Brune K. Acetaminophen (paracetamol) is a selective cyclooxygenase-2 inhibitor in man. FASEB J. 2008;22(2):383-90.

Högestätt ED, Jönsson BA, Ermund A, Andersson DA, Björk H, Alexander JP, Cravatt BF, Basbaum AI, Zygmunt PM. Conversion of acetaminophen to the bioactive N-acylphenolamine AM404 via fatty acid amide hydrolase-dependent arachidonic acid conjugation in the nervous system. J Biol Chem. 2005;280(36):31405-12.

Inamoto K, Kojima K, Nagamatsu K, Hamaguchi A, Nakata K, Nakamura H. A survey of the incidence of single-visit endodontics. J Endod. 2002;28(5):371-4.

Kim S. Neurovascular interactions in the dental pulp in health and inflammation. J Endod. 1990;16(2):48-53.

Mehlisch DR, Aspley S, Daniels SE, Bandy DP. Comparison of the analgesic efficacy of concurrent ibuprofen and paracetamol with ibuprofen or paracetamol alone in the management of moderate to severe acute postoperative dental pain in adolescents and adults: a randomized, double-blind, placebo-controlled, parallel-group, single-dose, two-center, modified factorial study. Clin Ther. 2010;32(5):882-95.

Menhinick KA, Gutmann JL, Regan JD, Taylor SE, Buschang PH. The efficacy of pain control following nonsurgical root canal treatment using ibuprofen or a combination of ibuprofen and acetaminophen in a randomized, double-blind, placebo-controlled study. Int Endod J. 2004;37(8):531-41.

Mickel AK, Wright AP, Chogle S, Jones JJ, Kantorovich I, Curd F. An analysis of current analgesic preferences for endodontic pain management. J Endod. 2006;32(12):1146-54.
Roane JB, Dryden JA, Grimes EW. Incidence of postoperative pain after single- and multiple-visit endodontic procedures. Oral Surg Oral Med Oral Pathol. 1983;55(1):68-72.

O'Keefe EM. Pain in endodontic therapy: a preliminary study. J Endod. 1976:2(10):315-9.

Olson NZ, Otero AM, Marrero I, Tirado S, Cooper S, Doyle G, Jayawardena S, Sunshine A. Onset of analgesia for liquigel ibuprofen 400 mg, acetaminophen 1000 mg, ketoprofen 25 mg, and placebo in the treatment of postoperative dental pain. J Clin Pharmacol. 2001;41(11):1238-47.

Roane JB, Dryden JA, Grimes EW. Incidence of postoperative pain after single-and multiple-visit endodontic procedures. Oral Surg Oral Med Oral Pathol. 1983:55(1):68-72.

Shimauchi H, Takayama S, Miki Y, Okada H. The change of periapical exudate prostaglandin E2 levels during root canal treatment. J Endod. 1997;23(12):755-8.

Siqueira JF, Barnett F. Interappointment pain: mechanisms, diagnosis, and treatment. Endodontic Topics 2004;7,93–109.

Torabinejad M, Cymerman JJ, Frankson M, Lemon RR, Maggio JD, Schilder H. Effectiveness of various medications on postoperative pain following complete instrumentation. J Endod. 1994;20(7):345-54.

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. Int Endod J. 2010;43(8):692-7.

Wells LK, Drum M, Nusstein J, Reader A, Beck M. Efficacy of Ibuprofen and ibuprofen/acetaminophen on postoperative pain in symptomatic patients with a pulpal diagnosis of necrosis. J Endod. 2011;37(12):1608-12.

Winter L Jr, Bass E, Recant B, Cahaly JF. Analgesic activity of ibuprofen (Motrin) in postoperative oral surgical pain. Oral Surg Oral Med Oral Pathol. 1978;45(2):159-66.

Appendix

MARQUETTE UNIVERSITY
Be The Difference.

Office of Research Compliance
Schroeder Complex, 102
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Milwaukee, Wisconsin 53201-1881
P 414.288.7570
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W www.marquette.edu/researchcompliance

December 9, 2011

Dr. Erik DeYoung
School of Dentistry

Dear Dr. DeYoung:

Your protocol number HR-2194, titled, "*Comparison of the Efficacy of Various Ibuprofen and Acetaminophen Regimens on the Treatment of Post-Endodontic Pain*," received full approval with contingencies on June 16, 2011 from the Marquette University Institutional Review Board, and final approval of all IRB requested changes on September 29, 2011. The Office of Research Compliance received the mandatory training documentation on December 8, 2011.

Your IRB approved consent form is enclosed with this letter. Use the stamped copies of this form when recruiting research participants. Each research participant should receive a copy of the stamped consent form for their records. Each participant must also sign a HIPAA Authorization form.

Subjects who go through the consent process are considered enrolled participants and are counted toward the total number of subjects, even if they have no further participation in the study. Please keep this in mind when conducting your research. This study is currently approved for 100 subjects.

If you need to increase the number of subjects, add research personnel, or make any other changes to your protocol you must submit an IRB Protocol Amendment Form, which can be found on the Office of Research Compliance web site: http://www.marquette.edu/researchcompliance/research/irbforms.shtml. All changes must be reviewed and approved by the IRB before being initiated, except when necessary to eliminate apparent immediate hazards to the human subjects. Any public advertising of this project requires prior IRB approval. If there are any adverse events, please notify the Marquette University IRB immediately.

Your approval is valid until June 15, 2012. Prior to this date, you will be contacted regarding continuing IRB review.

If you have any questions or concerns, please do not hesitate to contact me. Thank you for your time and cooperation.

Sincerely,

Amanda J. Ahrndt, RN, MS, MSN, CIM
IRB Manager & Interim Compliance Officer

cc: Dr. Christopher Okunseri, IRB Chair
Dr. Kris Olsen, DENT
Dr. Arthur Hefti, DENT

Enclosure