Efficacy of Ibuprofen and Ibuprofen/Acetaminophen on Postoperative Pain in Symptomatic Patients with a Pulpal Diagnosis of Necrosis

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Abstract

Introduction: The purpose of this prospective, randomized, double-blind study was to determine ibuprofen versus ibuprofen/acetaminophen use for postoperative endodontic pain in symptomatic patients with a pulpal diagnosis of necrosis and an associated periapical radiolucency who were experiencing moderate to severe preoperative pain. We also recorded escape medication use. **Methods:** Seventy-one adult patients presenting for emergency endodontic treatment with a symptomatic maxillary or mandibular tooth with a pulpal diagnosis of necrosis, periapical radiolucent area, and moderate to severe pain participated in this study. The patients were randomly divided into 2 groups by random assignment and numeric coding. An emergency debridement of the tooth was completed with hand and rotary instrumentation. At the end of the appointment, the patients randomly received capsules of either 600 mg ibuprofen or 600 mg ibuprofen combined with 1000 mg acetaminophen (blinded to both operator and patient). Patients also received a 6-day diary to be completed after anesthesia wore off and every morning for 5 days. Patients were asked to record pain, symptoms, and the number of capsules taken. Patients received escape medication (Vicodin) if the study medication did not control their pain. Postoperative data were analyzed by randomization test and step-down Bonferroni method of Holm. **Results and Conclusions:** There were decreases in pain levels and analgesic use over time for the ibuprofen and ibuprofen/acetaminophen groups. There was no statistically significant difference between the 2 groups for analgesic use or escape medication use. Approximately 20% of patients in both groups required escape medication to control pain. *(J Endod 2011;37:1608–1612)*

Key Words

Acetaminophen, ibuprofen, necrosis, postoperative pain

Symptomatic teeth with a pulpal diagnosis of necrosis are frequently treated in an endodontic practice. Removal of bacteria and necrotic debris by way of thorough canal debridement should reduce post-treatment discomfort by reducing bacteria and inflammatory mediators. Unfortunately, moderate to severe postoperative symptoms might persist after canal debridement, requiring the use of pain medication (nonsteroidal and narcotic medications) to help reduce postoperative pain (1–4).

Although there are a number of studies (1–21) of postoperative pain after endodontic treatment, they are not uniform in the assessment of pain. Some studies have evaluated the occurrence of interappointment emergencies (7, 8, 10, 14–16), intracanal medicament pain (11, 13, 21, 22), use of analgesics (17–20, 23), and effect of drainage on postoperative pain (4). Unfortunately, many of these studies have not separated the diagnosis of pulpal conditions (vital versus necrotic) and have only evaluated postoperative pain during short time intervals. Menhinick et al (12), Menke et al (19), and Mickel et al (23) have stressed the need for more studies of postoperative pain in endodontics that address medication use specific to the pulpal diagnosis and preoperative level of patients' pain.

Menhinick et al (12) found that a combination of acetaminophen and ibuprofen was more effective than ibuprofen alone in managing postoperative pain. However, their investigation included numerous pulpal conditions that might have differing postoperative courses.

Therefore, the purpose of this study was to determine ibuprofen versus ibuprofen/acetaminophen use for postoperative endodontic pain in symptomatic patients diagnosed with pulpal necrosis and associated periapical radiolucency who were experiencing moderate to severe preoperative pain.

Materials and Methods

Seventy-one adult patients participated in this study. All patients were in good health as determined by a health history and oral questioning. Exclusion criteria were as follows: subjects who were younger than 18 years; unable to take ibuprofen, acetaminophen, or hydrocodone; were allergic to local anesthetics or sulfites; were pregnant or nursing; were taking antibiotics; had a history of significant medical conditions (American Society of Anesthesiologists class II or higher); or were unable to give informed consent. The Ohio State University Human Subjects Review Committee approved the study, and written informed consent was obtained from each patient.

Patients included in this study had a clinical diagnosis of a symptomatic tooth with a pulpal diagnosis of necrosis and moderate to severe pain at the time of treatment. Each

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tooth tested negative to an electric pulp tester (Analytic Technology Corp, Redmond, WA) and to Endo-Ice (Hygenic Corp, Akron, OH) and had a periapical radiolucency of at least 2 mm by 2 mm on radiographic exam. All patients had no or very mild clinical swelling. No patients had a draining sinus tract.

Each patient rated his or her preoperative pain on a Heft-Parker visual analogue scale (VAS). The VAS was divided into 4 categories. No pain corresponded to 0 mm. Mild pain was defined as greater than 0 mm and less than or equal to 54 mm. Mild pain included the descriptors of faint, weak, and mild pain. Moderate pain was defined as greater than 54 mm and less than 114 mm. Severe pain was defined as equal to or greater than 114 mm. Severe pain included the descriptors of strong, intense, and maximum possible. To qualify for the study, patients presented with moderate to severe pain as rated on the VAS.

The patients received 1.8–5.4 mL of 2% lidocaine with 1:100,000 epinephrine (Xylocaine; AstraZeneca LP, Dentsply, York, PA) by infiltration or inferior alveolar nerve block. After local anesthesia was achieved, a rubber dam was placed, and an access opening was made. The working length was determined at 1 mm from the radiographic apex. The canals were prepared with hand and rotary instrumentation, and irrigation used 3% NaOCl. Each canal was filed to a size #20 file; then a crown-down technique was used to enlarge the coronal portion of the canal, then mid-root, and finally the apical third with rotary files (ProFile GTs 20/.12 through 20/.04; Denstply Maillefer, Ballaigues, Switzerland). The taper was stopped in each canal according to the original canal curvature and size, and then apical enlargement was completed in increasing sizes with K-type hand files until the canal was determined to be adequately cleaned and shaped. Each canal was irrigated with 2 mL of 3% NaOCl after the use of every third hand and rotary file by using a 25-gauge 5/8-inch needle with a Luer-Lok (Becton Dickinson, Franklin Lakes, NJ) attachment that was connected to a 20-mL disposable plastic Luer-Lok syringe. The canals were dried with sterile paper points, and $Ca(OH)_2$ (Multi-Cal; Pulpdent Corp, Watertown, MA) was placed as an intracanal medicament. The teeth were temporized with Cavit (Cavit G; 3M ESPE, Seefeld, Germany), and the patients were scheduled for root canal completion. No occlusal adjustments were done. The senior author (L.K.W.) provided all endodontic treatment.

After endodontic treatment, each patient was randomly assigned a medication bottle that contained the study medications and was labeled with a random number blinded to both the patient and the operator. A registered pharmacist compounded identical-appearing capsules of the ibuprofen/acetaminophen combination and ibuprofen (opaque purple size "0" capsules). The ibuprofen capsules were identical to the combination capsules, but they lacked the acetaminophen. All medications were placed in identical bottles so that they were indistinguishable to the investigator. A copy of the master list of 6-digit random numbers was supplied by the compounding pharmacist solely to the lead researcher (M.D.) and was not made available to anyone else during the data collection period.

The patients received a bottle containing either 80 capsules of 150 mg ibuprofen or 80 capsules of 150 mg ibuprofen/250 mg acetaminophen. The patients were then instructed to take 4 capsules every 6 hours as needed for pain.

If the medication given to the patient (ibuprofen or ibuprofen/acetaminophen) did not control their pain, the patients were instructed to call an assigned pager number that was carried by the investigator. The patients were instructed to not take any other pain medications during the investigation and that they could call the pager anytime. After speaking with the investigator, if an escape medication was needed, Vicodin 5/500 (hydrocodone/acetaminophen) was prescribed for the patient, and they were told to discontinue the study medications once they started the Vicodin to avoid taking multiple doses of acetaminophen (if they had received the acetaminophen medication). If the patient had significant swelling or fever, they were seen clinically, and proper management was rendered at that time. Antibiotics were prescribed as indicated.

Patients received a VAS, as described earlier, to record pain after anesthesia wore off. Resolution of anesthesia was determined by the patient through the loss of soft tissue numbness and/or the initiation of pain from the treated tooth. Patients recorded the time they perceived the anesthesia wore off and marked any pain that they were having on the VAS and any study medications they had taken. Patients also received a 5-day diary to record their experiences. On waking each morning, the patients recorded the date, time, any pain experienced, and the number and type (study or escape) of medication taken within each 24-hour period. There were sections for patient comments on the diary, and patients were required to return all unused medications on completion of the study to verify diary results.

The data from this study were collected and statistically analyzed. Comparisons between the combination ibuprofen/acetaminophen and ibuprofen groups for gender, jaw, and tooth type were analyzed by using the χ^2 test, and comparisons by age and initial pain were analyzed by using the randomization test. Differences in postoperative pain and medication usage were analyzed by using multiple randomization tests with *P* values adjusted by using step-down Bonferroni method of Holm. With a nondirectional alpha risk of 0.05, a sample size of 35 subjects per group was required to demonstrate a difference in the escape drug usage rate of ± 30 percentage points with a power of 0.80. Comparisons were considered significant if $P < .05$.

Results

Seventy-one subjects completed this study. Table 1 shows the preoperative variables. There were no statistically significant differences

TABLE 1. Preoperative Statistics for Ibuprofen and Ibuprofen/Acetaminophen Groups

	Ibuprofen group	Ibuprofen/acetaminophen group	*P* value
Subjects analyzed	36	35	
Gender	Female, 19/36 (53%) Male, 17/36 (47%)	Female, 15/35 (43%) Male, 20/35 (57%)	.4028
Age (mean ± SD), y	34.3 ± 14.0	37.3 ± 14.7	.3872
Initial pain* (mean ± SD), mm	130.1 ± 23.8	118.3 ± 22.3	.0377
Jaw	Maxillary, 20/36 (56%) Mandibular, 16/36 (44%)	Maxillary, 16/35 (46%) Mandibular, 19/35 (54%)	.4070
Tooth type	Anterior, 5 (14%) Molar, 25 (69%) Premolar, 6 (17%)	Anterior, 5 (14%) Molar, 21 (60%) Premolar, 9 (26%)	.6269

SD, standard deviation.

*There was a significant difference between the 2 groups.

TABLE 2. Pain by Day

Day	No. of subjects	Mean ± standard deviation (mm)	*P* value
0			
Ibuprofen	36	81.9 ± 40.9	.6812
Ibuprofen/acetaminophen	35	77.8 ± 44.9	
1			
Ibuprofen	36	62.7 ± 50.3	1.0000
Ibuprofen/acetaminophen	35	54.6 ± 43.4	
2			
Ibuprofen	30	30.8 ± 41.2	1.0000
Ibuprofen/acetaminophen	30	35.0 ± 35.4	
3			
Ibuprofen	29	17.9 ± 25.0	1.0000
Ibuprofen/acetaminophen	29	22.2 ± 27.9	
4			
Ibuprofen	29	13.1 ± 22.0	1.0000
Ibuprofen/acetaminophen	28	13.9 ± 22.8	
5			
Ibuprofen	29	6.5 ± 20.8	1.0000
Ibuprofen/acetaminophen	28	8.6 ± 15.7	

Day 0 = time when anesthesia wore off.

between the 2 groups with regard to gender, age, jaw, or tooth type. A statistically significant difference was observed in initial pain. However, all subjects in both groups reported moderate to severe preoperative pain.

Table 2 and Figure 1 show pain by day for the ibuprofen and ibuprofen/acetaminophen groups. There were no statistically significant differences between the 2 groups, and the pain ratings decreased over time.

Table 3 and Figure 2 demonstrate the number of capsules taken by day for both the ibuprofen and ibuprofen/acetaminophen groups. There were no statistically significant differences between the 2 groups.

The escape medication use for the ibuprofen and ibuprofen/acetaminophen groups is shown in Table 4. Nineteen percent of patients in the ibuprofen group and 20% of patients in the ibuprofen/acetaminophen group used an escape medication during the course of the study. There was no statistically significant difference between the 2 groups.

Discussion

Because there were no statistically significant differences for the effect of gender, age, jaw, or tooth type, these variables would be minimized between the 2 groups (Table 1).

A statistically significant difference was observed in initial pain. The ibuprofen group reported an initial pain of 130.1 mm (±23.8 mm), and the ibuprofen/acetaminophen group reported an initial pain of 118.3 mm (±22.3 mm) (Table 1). The difference in initial pain ratings between the 2 groups was 11.8 mm. An 11- to 12-mm difference within the moderate to severe range on a 170-mm scale might not be clinically meaningful, considering all patients had moderate to severe pain at presentation.

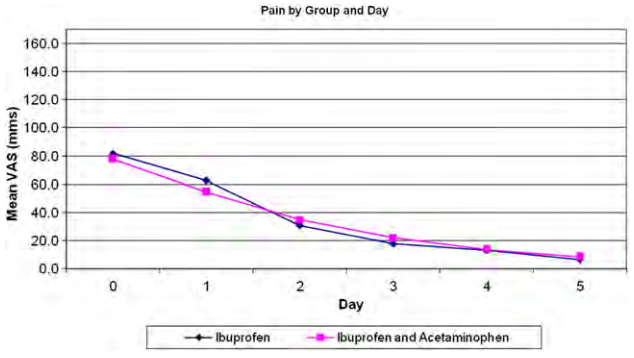

Figure 1. Pain by group and day.

There were no statistically significant differences in patient-reported pain between the 2 groups (Table 2 and Fig. 1). The decrease in tooth pain by increasing day is both logical and expected. We speculate that this is the natural course of the disease process for this clinical condition after debridement. It would have been beneficial to add a placebo group to the study, but refusing medication to a group initially presenting with moderate to severe pain would not be acceptable.

Table 3 and Figure 2 demonstrate medication use that followed a normal clinical course, with the most medication use in the first few days and decreasing use over time, paralleling the decreasing pain over time. However, the point of interest is that there were no statistically significant differences between the ibuprofen and ibuprofen/acetaminophen groups in medication use during any postoperative day.

As discussed in the article by Simpson et al (24), the mechanism of acetaminophen is unclear. It is purported to inhibit cyclooxygenase-1 and -2 and modulate the endogenous cannabinoid system by metabolism to AM404. It might also stimulate the descending serotonin pathways. The mechanisms of acetaminophen are partially different and might be complementary to ibuprofen, leaving potential for greater analgesic effects with combination dosing. However, because of the complex interaction of peripheral mediators and central effects, it is uncertain whether the combination would be superior in all treatment models.

Menhinick et al (12) compared 600 mg of ibuprofen with 600 mg ibuprofen/1000 mg acetaminophen combination and with a placebo in 57 patients with moderate to severe endodontic pain. They found the ibuprofen/acetaminophen combination to be the most successful when looking at an 8-hour postoperative period. Two of the 57 patients required a rescue medication (300 mg acetaminophen/30 mg codeine). However, their study differs from ours in that the follow-up was less than 24 hours, and only 19 of 57 patients were diagnosed with symptomatic teeth with a pulpal diagnosis of necrosis. The remaining patients were diagnosed with irreversible pulpitis.

Menke et al (19) studied patients with varying pulpal and periapical diagnoses. They compared 400 mg etodolac and 600 mg ibuprofen with a placebo in 36 patients postoperatively and at 4, 8, 12, 24, 48, and 72 hours. They found ibuprofen to be significantly better than etodolac and placebo for reducing pain 4 and 8 hours after the initiation of root

TABLE 3. Number of Study Capsules Taken

Drug	Day	No. of subjects	Mean no. of capsules	Standard deviation
Ibuprofen*	1	36	7.1	4.2
	2	30	3.7	4.3
	3	29	2.9	3.5
	4	29	1.4	2.9
	5	29	1.4	3.1
Ibuprofen/acetaminophen*	1	35	5.7	3.2
	2	30	4.5	5.1
	3	29	3.9	5.4
	4	28	1.6	3.5
	5	28	1.4	3.5

*There was no significant difference ($P > .05$) between the 2 groups.

canal therapy. Twenty-six percent of patients in their study required additional medication to control their postoperative pain. Fifty percent of the patients with a periapical diagnosis of acute apical periodontitis required additional medication. They found a significant difference by periapical diagnosis and need for additional medication. Gopikrishna et al (20) also studied the effect of pain medication on postoperative pain in patients with varying periapical diagnoses. They compared a single dose of 50 mg rofecoxib, 600 mg ibuprofen, and placebo and found no significant difference between rofecoxib and ibuprofen at 4 and 8 hours postoperatively. Both were significantly better than the placebo. They found that 53% of the patients with a periapical diagnosis of acute apical periodontitis required additional medication. They also found a significant relationship between the need for additional medication and the periapical diagnosis.

Merry et al (25) conducted a study comparing pain relief reported by patients who had been administered acetaminophen combined with ibuprofen, ibuprofen alone, or acetaminophen alone. Patients who were having 1 or more third molars extracted under general anesthesia or local anesthetic were advised to take 2 tablets before treatment and 2 tablets every 6 hours for up to 48 hours after treatment. Each dose included 1000 mg acetaminophen combined with 300 mg ibuprofen, 1000 mg acetaminophen, or 300 mg ibuprofen. Patients were given a 100-mm VAS for the 48 hours after treatment. Their conclusion was that the combination of acetaminophen with ibuprofen was a more effective pain reliever after third molar extractions when compared with acetaminophen alone and ibuprofen alone. This study differs from ours in the pain model (after extractions versus debridement) and the lower dosing of ibuprofen in the study by Merry et al.

Other studies have used surgical models to demonstrate a difference in combination drug efficacy versus 1 drug in single-dose studies spanning only 8 hours (26, 27). Mehlisch et al (27) found that the combination of 400 mg ibuprofen/1000 mg paracetamol had significantly better mean pain scores than 400 mg ibuprofen alone and the combination of 200 mg ibuprofen/500 mg paracetamol.

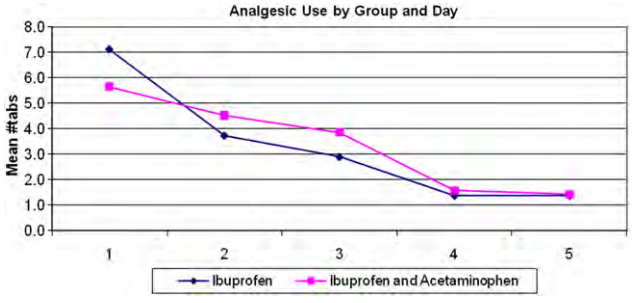

Figure 2. Analgesic use by group and day.

However, 200 mg ibuprofen/500 mg paracetamol did not have better mean pain scores than 400 mg ibuprofen alone. This offers the question of dose-dependent responses and how 600 mg ibuprofen alone would compare with the combination dosing. Moore et al (28) also found that combination drugs were more effective, but they did state that they were more effective "especially at lower doses". In a systematic review Ong et al (29) found that the combination of paracetamol and a nonsteroidal anti-inflammatory drug (NSAID) offered superior analgesia compared with either drug alone. Sniezek et al (30) compared acetaminophen with the combinations of acetaminophen/ibuprofen and acetaminophen/codeine for postoperative pain after Mohs micrographic surgery and reconstruction. They found the combination of acetaminophen/ibuprofen to be superior to either acetaminophen alone or acetaminophen/codeine for controlling postoperative pain.

The studies of the analgesic efficacy of a combination of acetaminophen with NSAIDs for postoperative pain clearly show the superiority of the combination over NSAIDs alone in acute pain models (25–30). However, the study of postoperative pain in third molar extraction models or similar acute pain models in which the patient presents with no or minimal pain is different than studying a model in which they present with moderate to severe pain and have endodontic treatment done. Only a few endodontic studies have addressed post operative analgesic efficacy, and these included diverse diagnostic categories. It might be that in the postoperative period for the specific subgroup of symptomatic endodontic patients in the current study, there might not be a clear superiority of the combination acetaminophen with an NSAID for pain relief. Further studies of postoperative analgesic efficacy in symptomatic patients with a pulpal diagnosis of necrosis who are experiencing moderate to severe preoperative pain are indicated.

Seven patients in each study group used an escape medication, with no significant difference between the groups (Table 4). Of these 14 patients, 7 required antibiotics because of the development of significant facial swelling (6 in the ibuprofen group, 1 in the ibuprofen/acetaminophen group). Therefore, the combination ibuprofen/acetaminophen or ibuprofen groups were not completely effective at controlling postoperative pain in these patients.

In conclusion, there was no statistically significant difference between the ibuprofen and ibuprofen/acetaminophen group for analgesic or escape medication use. There were average decreases in

TABLE 4. Escape Medication Usage

Escape medication used	Ibuprofen group	Ibuprofen/ acetaminophen group	*P* value
No	29/36 (81%)	28/35 (80%)	.9531
Yes	7/36 (19%)	7/35 (20%)	

pain levels and analgesic use over time. Approximately 20% of patients in both groups required escape medication to control pain.

Acknowledgments

The authors deny any conflicts of interest related to this study.

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