

---

# 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

K. A. Menhinick<sup>1</sup>, J. L. Gutmann<sup>2</sup>, J. D. Regan<sup>3</sup>, S. E. Taylor<sup>4</sup> & P. H. Buschang<sup>5</sup>

<sup>1</sup>Private Practice Limited to Endodontics, Washington, DC, USA; <sup>2</sup>Private Practice Limited to Endodontics, Dallas, TX, USA; <sup>3</sup>Department of Endodontics; <sup>4</sup>Oral and Maxillofacial Surgery/Pharmacology Department; and <sup>5</sup>Department of Orthodontics, Baylor College of Dentistry, Texas A&M University System Health Science Centre, TX, USA

---

## Abstract

**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. *International Endodontic Journal*, **37**, 531–541, 2004.

**Aim** To compare ibuprofen, to an ibuprofen/acetaminophen combination in managing postoperative pain following root canal treatment. It is hypothesized that the drug combination will provide more postoperative pain relief than the placebo or ibuprofen alone.

**Methodology** Patients presenting at the Texas A&M Baylor College of Dentistry's graduate endodontic clinic, experiencing moderate to severe pain, were considered potential candidates. Fifty-seven patients were included based on established criteria. Following administration of local anaesthesia, a pulpectomy was performed. The patients were administered a single dose of either: (i) placebo; (ii) 600 mg ibuprofen; or

(iii) 600 mg ibuprofen and 1000 mg of acetaminophen. Patients recorded pain intensity following treatment on a visual analogue scale and a baseline four-point category pain scale as well as pain relief every hour for the first 4 h then every 2 h thereafter for a total of 8 h. A general linear model (GLM) analysis was used to analyse the outcome.

**Results** Based upon the GLM analysis, there was a significant difference between the ibuprofen and the combination drug group, and between placebo and combination drug groups. There was no significant difference between the placebo and the ibuprofen.

**Conclusion** The results demonstrate that the combination of ibuprofen with acetaminophen may be more effective than ibuprofen alone for the management of postoperative endodontic pain.

**Keywords:** acetaminophen, ibuprofen, nonsurgical root canal treatment, postoperative pain control.

Received 2 April 2003; accepted 17 March 2004

---

## Introduction

Alleviating pain is of utmost importance when treating dental patients, as it is prevalent and has far reaching effects for both the patient and the clinician alike. Lipton *et al.* (1993) demonstrated that 12% of the 45 000 households surveyed in the United States

experienced at least one occurrence of tooth pain within the previous 6 months. In the UK a random sample of 4000 adults aged 18–65, with a 74% response rate showed an overall prevalence of orofacial pain of 26%. Forty-six per cent of the participants sought treatment and 17% had to take time off work (Macfarlane *et al.* 2002).

O'Keefe (1976) showed a significant relationship in endodontic patients between preoperative, operative, and postoperative pain levels. Patients presenting with extreme preoperative discomfort were more likely to

---

Correspondence: Dr James L. Gutmann, 1416 Spenwick Terrace Dallas, TX 75204, USA (e-mail: jlgutmann@earthlink.net).

have the same degree of discomfort both operatively and postoperatively. Moreover, postoperative pain was more likely to occur in these patients within the first 24 h period following root canal treatment (Harrison *et al.* 1983). Therefore, it is critical for the clinician to minimize or prevent pain by following appropriate treatment regimens supplemented with analgesics where indicated.

The major cause of pain is thought to be due to the release of inflammatory mediators that activate sensitive nociceptors surrounding the tooth (Johnsen *et al.* 1983). The resultant stimulation of both central and peripheral mechanisms (Malmberg & Yaksh 1992) is described as hyperalgesia and is defined as an increase in perceived magnitude of a painful stimulus (Dubner & Bennett 1983). Given the mechanisms that are occurring at the periphery, an anti-inflammatory agent should be used to control this process. One such medication is ibuprofen (IBU). It has been and still is one of the most widely used nonsteroidal anti-inflammatory drugs (NSAID) (Cooper *et al.* 1993). The use of ibuprofen, as well as other NSAID, in managing pain in patients with endodontic problems has been shown to be effective (Flath *et al.* 1987, Penniston & Hargreaves 1996, Rogers *et al.* 1999). A limitation to this drug, however, is what is referred to as the 'ceiling effect' (Desjardins & Cooper 1998). In spite of the administration of increased dosages of the medication the patient may not experience sufficient relief. Supplementing the initial dosage with a second drug that acts in an alternative manner may allow sufficient analgesia to be achieved.

Another commonly used analgesic to control dental pain is acetaminophen. Although its use dates back a number of years its mechanism of action is not yet fully understood. What is known is that it is a weak inhibitor of peripheral prostaglandin synthesis and that it is in some way active in the central nervous system (CNS). This action may be via the inhibition of central hyperalgesia, induced by pain-producing neurotransmitters, such as substance P or the excitatory amino acid glutamate (Bjorkman *et al.* 1994). There is also some evidence of its effect on the COX-dependent mechanisms (Bjorkman 1995, Chandrasekharan *et al.* 2002). If this is the case then a combination of acetaminophen with a medication that is effective in the periphery may create a scenario whereby sufficient analgesia is obtained without having to add an opioid, thereby avoiding unnecessary side effects.

In a recent randomized, double-blind, oral surgical study (Breivik *et al.* 1999) the combination of acetami-

nophen and a nonsteroidal anti-inflammatory provided superior and prolonged analgesia with fewer side effects when compared with acetaminophen and codeine. The combination of acetaminophen and an NSAID also demonstrated improved pain control compared with either drug used separately. Whilst the benefits and efficacy of combining medications to deal with dental pain have been detailed (Dionne 2000), there have been no controlled dental studies evaluating the additive effects of combining an NSAID with acetaminophen apart from a recent report by Breivik *et al.* (1999). The endodontic literature indicates a deficiency in the evaluation of the use of drug combinations to prevent or manage pain, especially as it relates to nonopioids.

The purpose of this double-blind, prospective pain study was to compare ibuprofen, used commonly to control postoperative endodontic pain, against a combination of ibuprofen and acetaminophen or a placebo. It is hypothesized that the drug combination will be more effective at controlling postoperative pain than the placebo or ibuprofen alone.

## Materials and methods

Patients were selected from those that presented to the Texas A&M University System Health Science Center Baylor College of Dentistry's emergency clinic. General information was obtained from a 'prescreening' form. Patients were considered potential candidates if they had moderate to severe spontaneous pain of odontogenic origin (50–100 mm on a visual analogue scale, VAS). Following assignment to a graduate endodontic resident, the patient was given more details of the study. Strict inclusion and exclusion criteria were then applied to determine if the patient was a potential participant.

The *inclusion* criteria for the study were:

- 1 Patient reports spontaneous pain ranging from 50 to 100 mm on a VAS (0–100 mm);
- 2 Patient chooses to have root canal treatment for pain of endodontic origin;
- 3 The patient presented with American Society of Anesthesiologists (ASA) I or II medical history (ASA 1963);
- 4 The patient had read and thoroughly understood the questionnaires written in English;
- 5 Informed consent was obtained from patient;

Patients were *excluded* if they fell into any of the following categories:

- 1 Younger than 18 years of age;
- 2 Analgesic taken within the last 4 h;

- 3 History of allergy to NSAIDs, aspirin or local anaesthetics;
- 4 History of gastrointestinal (GI) disorders, oesophageal reflux, active asthma, decreased hepatic function, haemorrhagic disorders, or poorly controlled diabetes mellitus.
- 5 The patient is currently taking opioids, monoamine oxidase inhibitors, tricyclic antidepressants, carbamazepine, diuretics, or anticoagulants;
- 6 There is history of opioid addiction or abuse; and
- 7 The patient was pregnant or nursing.

If the patient met all the inclusion criteria they were invited to participate in the study. A total of 65 patients signed a consent form outlining the procedure and its possible risks. The study was approved through the Baylor College of Dentistry's Institutional Review Board (IRB) for human studies.

All endodontic procedures performed by the graduate endodontic residents were standardized. Provisional pulpal and periradicular diagnoses were determined after clinical and radiographic examination by the graduate endodontic resident. Anaesthesia was obtained with 2% lidocaine with 1 : 100 000 epinephrine followed by rubber dam isolation, access, identification and instrumentation of the major canals. Residents primarily used rotary nickel titanium instruments, in a modified-crown down technique, along with stainless steel hand instruments as necessary based on canal anatomy and patency. Cleaning and shaping was considered as minimally adequate when an ISO file size 25 with a .04 taper came to within 0.5–1.0 mm of estimated working length, which was determined from the preoperative radiograph. Copious irrigation with 5.25% sodium hypochlorite and 17% liquid EDTA (Roth International, Chicago, IL, USA) were used between each file with the irrigant remaining in the canal during the entire procedure. A canal lubricant, Glyde (Tulsa Dental Products, Tulsa, OK, USA), was used to facilitate instrumentation. When instrumentation was completed the canals were rinsed thoroughly and dried with paper points. A cotton pellet was placed in the access cavity, which was restored with intermediate restorative material (IRM) (Tulsa Dental Products) and the occlusion checked. No intracanal medicament was placed.

A randomized, double-blind, placebo-controlled protocol was followed. A licensed pharmacist from the Baylor Health Science's Center prepared the following drug groups: 600 mg ibuprofen (Par Pharmaceutical, Inc., Spring Valley, NJ, USA), 600 mg of ibuprofen plus 1000 mg of acetaminophen (United Research

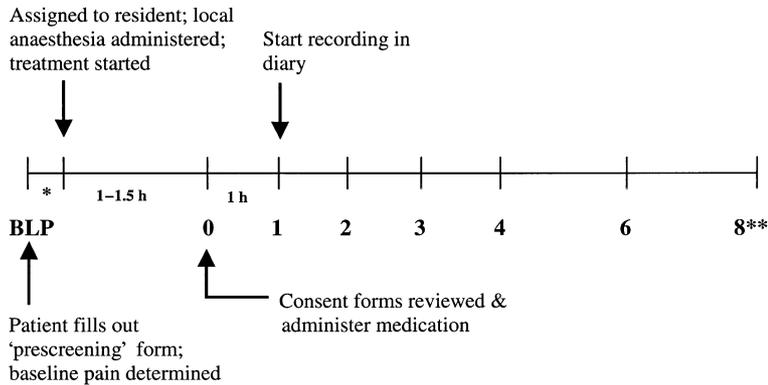
Laboratories, Inc., Philadelphia, PA, USA) or the lactose placebo (Spectrum Chemical Mfg. Corp., New Brunswick, NJ, USA). These were then placed in clear, unmarked, indistinguishable, gelatine capsules size 00 (Shionogi Qualicaps, Inc., Whitsett, NC, USA) with lactose added to take up the remaining space in the capsules. Patients were randomized using the Microsoft 2000 Excel program randomization software.

Following completion of root canal treatment, the primary investigator reviewed the consent forms with the patients, and a single dose of the test drug was administered. Patients then received a pain diary (written in English) and a 'rescue medication' that consisted of eight tablets of acetaminophen 300 mg plus codeine phosphate 30 mg (Ortho-McNeil Pharmaceutical, Inc., Raritan, NJ, USA) with instructions written on the package. If patients were to experience pain that was not managed by the test drug the patients then had access to additional analgesics. Strict instructions, however, were given to the patient not to take the rescue medication until first speaking with the investigator or the resident on-call. If the rescue medication was not taken, the patient was told to return it at their next appointment.

Within each package of rescue medication was a card corresponding to the test drug groups. In the event of experiencing pain not tolerable to the patient they were instructed to call the investigator or the resident on-call. The patient was then requested to look in the rescue drug package for one of these numbers. The drug group was determined and the appropriate recommendation made for analgesic therapy. If the rescue analgesic was taken the last recorded observations for all four questions was then carried forward for the remainder of the 8-h observation period (Laska *et al.* 1991).

The diary contained two pain scales (VAS and a baseline four-point scale), a pain relief scale and an overall effectiveness scale, as well as a table to record any side effects that may have been experienced. The diary was designed so patients would make entries every hour for the first 4 h after taking the medication and then every 2 h thereafter for a total of six entries or 8 h (Fig. 1). Patients were contacted by the investigator that evening to review the case report forms and answer or explain any unclear issues the patient may have had at the that time. Upon completion the diary was mailed back to the investigator.

Analysis of the VAS and baseline four-point pain distributions showed significant departures from normality and a  $\log_{10}$  transformation was executed. The



\*Approximately 15 – 30 min  
 \*\*Hours following administration of medication  
 BLP = Baseline pain

**Figure 1** Study time line.

general linear model (GLM) for repeated measures was used to evaluate group differences, changes over time, and group differences in changes over time (i.e. interactions between group and time), group differences were further analysed using the *post-hoc* least squared difference (LSD) test. Baseline pain measurements were compared with the measurements made immediately after treatment using GLM. A difference was considered significant if the probability that it occurred to chance alone was <5% (i.e.  $P < 0.05$ ). The statistical analyses were performed with the Statistical Package for Social Sciences, version 8.0 (SPSS Inc., Chicago, IL, USA).

**Results**

Over a period of 18 months 93 patients were screened for possible participation in the study. Sixty-five fulfilled the inclusion criteria and consented to participate. Eight patients did not return the diaries, therefore a total of 57 were included. Similarities between treatment groups, including patient demographics, baseline pain (Table 1), pulpal (Table 2) and periradicular diagnoses (Table 3), as well as teeth treated (Table 4) were evaluated. As illustrated in Tables 2–4 the treatment groups were similar for the distribution of preoperative pulpal and periradicular diagnoses and teeth treated. Baseline pain was measured using a VAS and are listed in Table 1.

In the 8 h following treatment only five patients required additional analgesia: three patients from the placebo group, one from the IBU group and one from

the combination drug group. After speaking with the investigator, the patients were given the option of taking the ‘rescue medication’ (1–2 tablets 300 mg acetaminophen +30 mg codeine) or an over-the-counter analgesic. Two chose to take the rescue medication whilst the others chose over-the-counter medications. All five of these patients had a preoperative diagnosis of

**Table 1** Demographics and clinical features

	Placebo (n = 19)	600 mg IBU (n = 20)	600 mg IBU + 1000 mg APAP (n = 18)
Gender			
Women	11	14	16
Men	8	6	2
Age (years)			
Mean	42	40	35
Range	24–80	21–61	19–58
Baseline pain intensity (VAS), mean ± SD	80 ± 3.9	69 ± 3.8	81 ± 4.2

**Table 2** Distribution of pulpal diagnoses amongst the three treatment groups

Group	n	Irreversible pulpitis	Necrosis
Placebo	19	14 (74)	5 (26)
IBU	20	14 (70)	6 (30)
IBU + APAP	18	10 (56)	8 (44)

Values in parentheses are in percentage.

**Table 3** Distribution of periradicular diagnoses amongst the three treatment groups

Group	n	Normal	APP <sup>a</sup>	CPP <sup>b</sup>	AAA <sup>c</sup>	Subacute PP <sup>d</sup>
Placebo	19	1 (5)	17 (89)	1 (6)	0	0
IBU	20	1 (5)	16 (80)	2 (10)	0	1 (5)
IBU + APAP	18	0	17 (94)	1 (6)	0	0

Values in parentheses are in percentage.

<sup>a</sup>Acute periradicular periodontitis: Inflammation usually of the apical periodontium producing clinical symptoms including painful response to biting, palpation and percussion (AAE 1998).

<sup>b</sup>Chronic periradicular periodontitis: Inflammation and destruction of apical periodontium that is of pulpal origin, appears as a periradicular radiolucent area and does not produce clinical symptoms (AAE 1998).

<sup>c</sup>Acute alveolar abscess: An inflammatory reaction to pulpal infection and necrosis characterized by rapid onset, spontaneous pain, tenderness of the tooth to pressure, pus formation and eventual swelling of associated tissues (AAE 1998).

<sup>d</sup>Subacute periradicular periodontitis: Inflammation of the apical periodontium producing mild clinical symptoms to biting, palpation or percussion below levels considered as acute.

**Table 4** Teeth treated

Group	Maxillary			Mandibular		
	Anterior	Premolar	Molar	Anterior	Premolar	Molar
Placebo	2	2	4	0	2	9
IBU	2	3	7	0	0	8
IBU + APAP	3	4	5	0	1	5

irreversible pulpitis and a periradicular diagnosis of acute periradicular periodontitis.

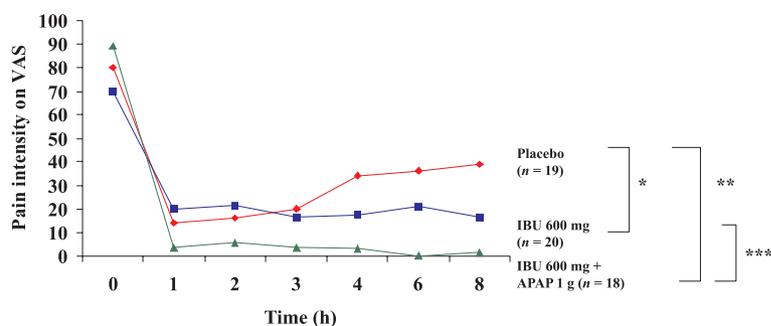
The primary efficacy measure for the study was pain intensity. Median pain intensity values for each treatment group are represented in Fig. 2. All groups displayed a significant ( $P < 0.001$ ) reduction in pain from baseline to the first hour after administration of the medications. The percentage reduction in pain for the placebo was 71%, IBU 76% and IBU + APAP 96%. The GLM analyses concluded that there was a significant group difference ( $P = 0.026$ ). *Post-hoc* comparisons using the LSD test determined a significant difference between IBU + APAP and the placebo ( $P = 0.009$ ) as well as between the IBU and IBU + APAP ( $P = 0.047$ ). The IBU and placebo groups were not significantly different ( $P = 0.481$ ).

There was no significant change over time ( $P = 0.981$ ) and no interaction between group and time ( $P = 0.932$ ). Mean pain intensity values for each group over the 8-h time period is listed in Table 5.

The 4–8-h time periods, which were also evaluated using the GLM analyses, demonstrated statistically significant group differences ( $P = 0.005$ ), no significant change during this time period and no group interaction. *Post-hoc* comparison showed IBU + APAP to be significantly different than the placebo ( $P < 0.001$ ) and the IBU group ( $P = 0.025$ ).

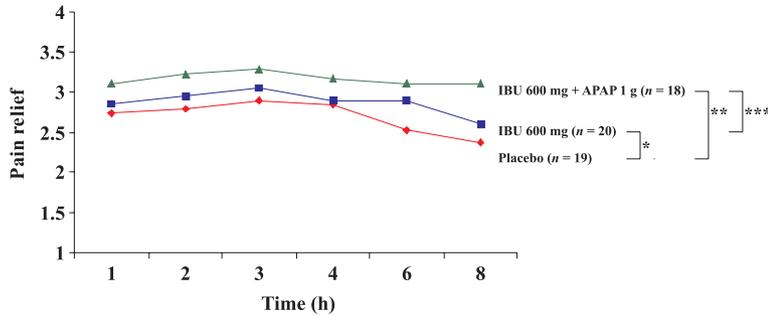
Pain intensity was also measured using the baseline four-point scale and produced similar results to the VAS. The GLM analyses showed that group differences in pain intensity approached significant levels

**Figure 2** Median pain intensity values rated on a 100 mm visual analogue scale (VAS) at each time period. IBU, ibuprofen; APAP, acetaminophen. \* $P = 0.481$ ; \*\* $P = 0.009$ ; \*\*\* $P = 0.047$  (GLM, general linear model).

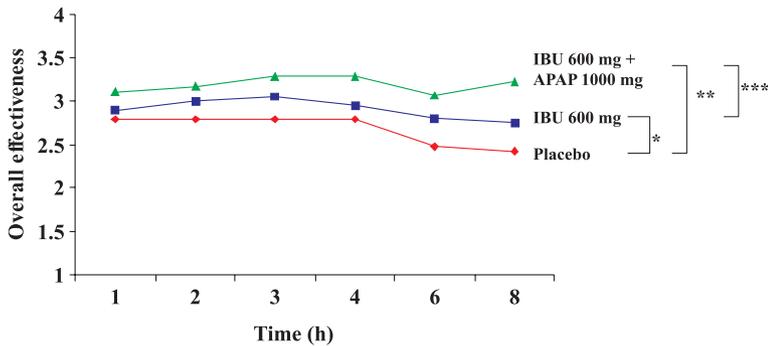


**Table 5** Mean of all VAS values during 8 h (with 95% confidence intervals) according to a general linear model analysis

	Placebo	IBU 600 mg	IBU 600 mg + APAP 1000 mg
Placebo	32 (22–48)	$P = 0.481$	$P = 0.009$
IBU 600 mg	$P = 0.481$	17 (11–21)	$P = 0.047$
IBU 600 mg + APAP 1000 mg	$P = 0.009$	$P = 0.047$	3 (0–6)



**Figure 3** Mean pain relief score at each time period after medication has been taken. Pain relief scores were rated on the following categorical scale: 1 = none; 2 = mild; 3 = moderate and 4 = excellent. IBU, ibuprofen; APAP, acetaminophen.  $*P = 0.547$ ;  $**P = 0.145$ ;  $***P = 0.304$  (GLM).



**Figure 4** Mean overall effectiveness of the medication as measured over time. Effectiveness was measured on the following categorical scale: 1 = poor; 2 = fair; 3 = good; 4 = excellent. IBU, ibuprofen; APAP, acetaminophen.  $*P = 0.434$ ;  $**P = 0.117$ ;  $***P = 0.407$  (GLM).

( $P = 0.060$ ). Pair-wise comparisons showed that the IBU + APAP was significantly different than the placebo ( $P = 0.020$ ), the IBU and the placebo were not significantly different from one another ( $P = 0.448$ ), nor was the IBU when compared with IBU + APAP ( $P = 0.102$ ). There were no significant changes over time ( $P = 0.643$ ), or interactions between group and time ( $P = 0.997$ ).

A secondary efficacy measure was pain relief. Mean pain relief versus time for each group is shown in Fig. 3. There were no significant differences in pain relief between groups ( $P = 0.339$ ), there were no significant changes over time ( $P = 0.055$ ), and there were no significant interactions between group and time ( $P = 0.951$ ). Mean overall effectiveness of the medication (Fig. 4) also showed no significant group differences ( $P = 0.289$ ), no significant change over time ( $P = 0.104$ ) and no significant group and time interaction ( $P = 0.926$ ).

The patients also recorded any adverse effects during the 8 h following treatment (Table 6). Of the 57 participants, a total of 23 reported adverse side effects. The placebo group experienced the highest degree of CNS (53%) and GI (21%) symptoms. Headache and nausea were the most commonly reported GI and CNS side effects. Reporting of adverse side effects in the other two groups appeared significantly lower than the placebo. Furthermore, there were reports of increased

**Table 6** Adverse side effects

Group	<i>n</i>	GI	CNS	Other
Placebo	19	4 (21)	10 (53)	0
IBU	20	1 (5)	6 (30)	3 (15)
IBU + APAP	18	1 (6)	5 (28)	0

Values in parentheses are in percentage. GI = nausea, emesis; CNS = headache, dizziness, drowsiness; Other = sweating, rash, wheezing, tightness in chest.

sweating from the IBU group, but this was the only complaint from the 'other' category. No serious adverse events occurred at any point in time during the 8-h following treatment.

## Discussion

The present study was conducted in a prospective manner. The advantages of conducting prospective studies include: (1) direct evaluation of the incidence; (2) an efficient method of investigating possible correlations between disease and associated factors; and (3) less susceptibility to observer respondent biases. Prospective studies however, do have disadvantages, as they tend to be more costly, are more time consuming and are more difficult to conduct (Schwartz & Lellouch 1967).

Other challenges involved with a prospective study are controlling for variables such as the operators involved in treatment and local anaesthetic administration. A number of operators were involved in the treatment phase in order to ensure an adequate sample size. Schwartz & Lellouch (1967) have referred to studies such as this one as 'pragmatic clinical trials' and may more accurately reflect a realistic clinical setting. Local anaesthetic administration and metabolism may also introduce further variability. Operators were not limited in the amount of anaesthesia they could administer and more anaesthesia may have been required in particular patients. However, the half-life of lidocaine 2% with epinephrine 1 : 100 000 in the soft tissue is 3–4 h (Malamed 1986), therefore, by the time the patients had reached the second diary entry its effects should have worn off substantially.

Whilst a number of prospective analgesic-type dental pain control studies exist, there is a lack of prospective studies specifically evaluating the combination of an NSAID with acetaminophen. Breivik *et al.* (1999) using a third molar extraction model, provides the only other well-controlled dental study evaluating this combination of drugs. The combination of acetaminophen and an NSAID provided superior and prolonged analgesia with fewer side effects when compared with the combination of acetaminophen and codeine. The combination of acetaminophen and an NSAID also demonstrated superior pain control in comparison with that achieved when either drug was used separately. This finding is significant because the main disadvantages of the use of narcotics are their potential for abuse, their CNS side effects, as well as minimal peripheral activity.

A review by Hyllested *et al.* (2002) also examined a significant number of both medical and dental studies, and the comparative effects of paracetamol, NSAIDs or their combination in postoperative pain management. Overall, in major surgery, gynaecological as well as orthopaedics, the use of NSAIDs and acetaminophen did not produce a substantial difference in pain control. In dental surgery, NSAIDs proved to be more effective, however, there was the suggestion that the combination of an NSAID with acetaminophen provided enhanced analgesic efficacy when compared with either drug alone. No endodontic studies were considered in the Hyllested *et al.* (2002) review, as any that used paracetamol or ibuprofen were flawed either statistically or in their method of randomization.

In addition to the Breivik *et al.* (1999) study there is only one other double-blind, oral surgical study administering the combination of voltarol (diclofenac) and acetaminophen. Matthews *et al.* (1984) evaluated a single dose of 50 mg voltarol with or without 500 mg acetaminophen in 28 patients experiencing pain post-surgically. There was no significant difference found amongst any of the groups. There was no significant difference between the placebo and 500 mg acetaminophen group. The result questions the sensitivity of the analgesic assay used in this study as well as the low dose of acetaminophen administered.

The inclusion of a placebo group when conducting these types of studies is of significant clinical relevance. Previous endodontic studies have concluded that definitive dental treatment without the administration of medication may enhance pain relief significantly (Hasselgren & Reit 1989, Oguntebi *et al.* 1992). Results from the present study emphasize this point, showing a mean reduction of 71% in the placebo group from the VAS baseline pain to the VAS measurements recorded in the 8 h following treatment. This stresses the importance of definitive dental care where possible and that it should be incorporated as an effective treatment strategy for the management and prevention of pain. In comparison, IBU and the IBU + APAP group reported mean pain intensity reductions of 76 and 96%, respectively.

Pain intensity decreased significantly in all three groups following treatment. When comparing the placebo with 600 mg ibuprofen (IBU) there was no significant difference in pain intensity or pain relief. This result strongly suggests that definitive treatment (pulpectomy) allowed for an adequate reduction in pain intensity. Our finding of a significant difference between the ibuprofen and the combination drug group agrees

with that of Breivik *et al.*'s (1999) study and may also add additional support for the combination of these two drugs to manage pain of a different model. There was a significant difference between the combination group and the placebo. This is not surprising, as one would expect this result simply due to the analgesic efficacy of the medications and the nature of the ongoing acute pain processes.

The consistency of the pain intensity and pain relief measurements and their substantially lowered levels over the 8-h time period is of interest. The pattern observed for the placebo group demonstrates a marginal increase from time period 4 through to the end of the recording period. This result would be consistent with the local anaesthetic simply losing its effect, whereas the other treatment groups remained at their respective levels possibly due to the effects of the medication. Statistical analysis for this time period demonstrated the placebo group was significantly different than the combination with no difference existing between the placebo and the ibuprofen groups. However, the combination drug group was significantly different from the ibuprofen alone, appearing to suggest that the combination of drugs may continue to provide analgesia for 8 h after the procedure relative to the placebo and ibuprofen. One would expect at the later time periods to see a possible increase in pain as the full effect of the medications should be decreasing significantly. It is well established that the elimination half-life of ibuprofen is 2 h and acetaminophen is 2–4 h (Clissold 1986, Day *et al.* 1987, Evans 1992). Patients may not be truly measuring accurately at these later time periods or it could be that the patients feel obliged to register a value and feel that it's easier to record the same response that they had placed 1-h prior. Suggestions for other ways to measure the pain may be to use the McGill Pain Questionnaire (Katz & Melzack 1999), or perhaps ask the questions in a different fashion at each of the time periods. The significant decrease in pain from the initial recordings, that remained substantially lowered throughout in the placebo group may be explained either by a postplacebo response (placebo effect) or perhaps it was due solely to the treatment.

Sample size may also have influenced the results of this study. The original estimation of a statistically significant sample size was calculated to be 60. Only 57 patients were included due to time constraints. It is possible that with an increase in sample size the results would have been more definitive. When examining oral surgical studies, the ranges in patient sample size vary

from as high as 400 to less than 60. The sample size of this study could have been larger but is still comparable when evaluating other endodontic pain studies.

The insignificant result between the placebo and 600 mg of ibuprofen may be due to the aforementioned issues. However, the patients may have truly felt significant pain relief from the pulpectomy alone whether they received an analgesic or not. In addition, the technique used to instrument the teeth may be a factor contributing to this result. All operators used the modified crown-down technique primarily with the use of rotary instrumentation. This technique produces less extrusion of debris apically (Ruiz-Hubard *et al.* 1987, Reddy & Hicks 1998) and with less extrusion of debris there is a decreased chance for an inflammatory response and hence, a decrease in postoperative pain. This could explain the similarities in pain intensity and relief of the placebo and IBU groups. A strong placebo effect may also contribute to this result.

In order to control for variables that may have affected the response to the placebo, the medications administered were not given the appearance, nor was it suggested to the patient that they were more effective. Buckalew & Coffield (1982) demonstrated that larger capsules tend to be viewed as stronger, yellow capsules tend to be perceived as stimulants or antidepressants, whilst white capsules tend to be perceived as analgesics or narcotics. All capsules were clear with the placebo and analgesics appearing as a white powder inside the capsules. It may be speculated that the patients may have interpreted the placebo as being an analgesic, as suggested by Buckalew & Coffield (1982).

The mechanisms of action of the NSAIDs and acetaminophen are by no means similar. NSAIDs are most effective by affecting the synthesis of prostaglandins by way of inhibition of the cyclooxygenase enzymes. They also have been found to interact with CNS opioid and nitric oxide mechanisms (Malmberg & Yaksh 1992, Bjorkman 1995). However, acetaminophen acts by inhibiting prostaglandin synthesis in the CNS (Muth-Selbach *et al.* 1999) and by interacting with serotonin and nitric oxide mechanisms (Bjorkman 1995). Studies by Bannwarth *et al.* (1992) and Piletta *et al.* (1991) have demonstrated the ability of the drug to cross the blood–brain barrier. This may then allow for the inhibition of central hyperalgesia that is induced by pain-producing neurotransmitters-substance P or the excitatory amino acid glutamate (Hunnskaar *et al.* 1985, Bjorkman *et al.* 1994, Bjorkman 1995). In addition, test tube experiments performed almost 30 years ago showed the acetaminophen might

selectively target COX receptors present in the brain (Flower & Vane 1972). Chandrasekharan *et al.* (2002) may have come closer to addressing this dilemma by locating a variant of COX-1 in the brain. They speculate that a COX-3 may in fact exist that is especially sensitive to acetaminophen and related compounds. Given that the two drugs have different mechanisms of action perhaps when combined they produce a synergistic response. In this case the difference between the IBU group and the IBU + APAP was significantly different which might suggest such a response, however, due to the lack of an acetaminophen group alone one can only infer a positive interaction when the drugs are combined.

The degree of side effects was higher in both the GI and the CNS in the placebo group in comparison with the other two. Placebos have been shown to have side effects such as drowsiness, headaches, nervousness, insomnia, nausea, and constipation (Pogge 1963). A more likely explanation in this case however, may be the continuation of preexisting symptoms. Comparing the other two treatment groups and the possibility for side effects, acetaminophen is found to have less overall side effects when compared with NSAIDs (Lesko & Mitchell 1995), and only with prolonged administration of NSAIDs is there the potential for gastric haemorrhaging or intestinal ulcer formation. Therefore, patients in the placebo group reporting side effects, especially CNS symptoms, may have reported them simply because they did not receive any form of medication. Only one patient from the IBU group reported incidences of sweating. After further discussion the patient was unsure if this was due to the medication or the fact that he 'wasn't feeling well'.

There were no untoward events throughout the study and only five patients required additional analgesic intervention; three patients from the placebo group, one from the IBU group and one from the IBU + APAP group. Two patients chose to take the 350 mg of acetaminophen with 30 mg of codeine (rescue medication), whereas the other three selected maximal dosages of either ibuprofen or acetaminophen. The majority of patients did not feel that their pain was adequately severe and warranted a narcotic in addition to another analgesic.

A greater number of females than males were treated in this study. Women are more likely to report severe pain, and will seek treatment more readily than men (Unruh 1996, Dao & LeResche 2000). How this affects the overall results of this study is difficult to assess.

Statistical analysis of the effects of sex on the effectiveness of the analgesic administered was unable to be conducted due to the large number of women in both the IBU and combination groups. No sex effect has been found when comparing the analgesic response with ibuprofen using the third-molar extraction dental pain model (Averbuch & Katzper 2000). Furthermore, no difference with respect to gender and response to a placebo has been found (Averbuch & Katzper 2001). It is however possible that due to the greater number of females treated and the basic biological differences between males and females that gender could have played a role in the response to the medications, thereby affecting the result.

There are possible therapeutic implications as to the outcome of this study. Currently, NSAIDs are extremely beneficial in managing postoperative pain in dentistry (Flath *et al.* 1987, Penniston & Hargreaves 1996, Rogers *et al.* 1999). However, there may be occasions when additional analgesia is required. The outcome of this study suggests that the combination of ibuprofen and acetaminophen was more effective at reducing postoperative pain than ibuprofen alone. It is important to stress that the use of a model that is prospective, randomized, double-blind, and placebo-controlled adds credibility to the outcome. More research using this model and analgesic combination would be useful as the administration of definitive dental treatment with appropriate analgesics is a significant area in the management of the endodontic pain patient.

## Acknowledgements

Grants from the American Association of Endodontists Research Foundation and an intramural grant from the Baylor College of Dentistry supported this research. We gratefully acknowledge the contributions of Dr Ken Hargreaves, Charlotte Binette, as well as, the graduate endodontic residents from Texas A&M Baylor College of Dentistry.

## References

- AAE (1998) *Glossary – Contemporary Terminology for Endodontics*, 6th edn. Chicago, IL: American Association of Endodontists.
- ASA (1963) New classification of physical status. *Anesthesiology* **24**, 111.
- Averbuch M, Katzper M (2000) Baseline pain and response to analgesic medications in the postsurgery dental pain model. *Journal of Clinical Pharmacology* **40**, 133–7.

- Averbuch M, Katzper M (2001) Gender and the placebo analgesic effect in acute pain. *Clinical Pharmacology and Therapeutics* **70**, 287–91.
- Bannwarth B, Netter P, Lopicque F (1992) Plasma and cerebrospinal fluid concentrations of paracetamol after a single intravenous dose of propacetamol. *British Journal of Clinical Pharmacology* **34**, 79–81.
- Bjorkman R (1995) Central antinociceptive effects of non-steroidal anti-inflammatory drugs and paracetamol. Experimental studies in the rat. *Acta Anaesthesiologica Scandinavica Supplementum* **103**, 1–44.
- Bjorkman R, Hallman KM, Hedner J, Hedner T, Henning M (1994) Acetaminophen blocks spinal hyperalgesia induced by NMDA and substance P. *Pain* **57**, 259–64.
- Brevik EK, Barkvoll P, Skovlund E (1999) Combining diclofenac with acetaminophen or acetaminophen-codeine after oral surgery: a randomized, double-blind single-dose study. *Clinical Pharmacology and Therapeutics* **66**, 625–35.
- Buckalew LW, Coffield KE (1982) An investigation of drug expectancy as a function of capsule color and size and preparation form. *Journal of Clinical Psychopharmacology* **2**, 245–8.
- Chandrasekharan NV, Dai H, Roos KL *et al.* (2002) COX-3, a cyclooxygenase-1 variant inhibited by acetaminophen and other analgesic/antipyretic drugs: cloning, structure, and expression. *Proceedings of the National Academy of Sciences of the United States of America* **99**, 13926–31.
- Clissold SP (1986) Aspirin and related derivatives of salicylic acid. *Drugs* **32** (Suppl. 4), 8–26.
- Cooper SA, Quinn PD, MacAfee K, Hersh EV, Sullivan D, Lamp C (1993) Ibuprofen controlled-release formulation. A clinical trial in dental impaction pain Oral Surgery. *Oral Medicine and Oral Pathology* **75**, 677–83.
- Dao TT, LeResche L (2000) Gender differences in pain. *Journal of Orofacial Pain* **14**, 169–84 (discussion 84–95).
- Day RO, Graham GG, Williams KM, Champion GD, de Jager J (1987) Clinical pharmacology of non-steroidal anti-inflammatory drugs. *Pharmacology and Therapeutics* **33**, 383–433.
- Desjardins P, Cooper SA (1998) Peripherally acting analgesics and antipyretics. In: NE Yagiela JA, Dowd FJ, eds. *Pharmacology and Therapeutics for Dentistry*. St Louis, MO: Mosby-Year Book, pp. 281–96.
- Dionne R (2000) Additive analgesia without opioid side effects. *Compendium of Continuing Education in Dentistry* **21**, 572–4, 6–7.
- Dubner R, Bennett GJ (1983) Spinal and trigeminal mechanisms of nociception. *Annual Reviews in Neuroscience* **6**, 381–418.
- Evans AM (1992) Enantioselective pharmacodynamics and pharmacokinetics of chiral non-steroidal anti-inflammatory drugs. *European Journal of Clinical Pharmacology* **42**, 237–56.
- Flath RK, Hicks ML, Dionne RA, Pelleu GB (1987) Pain suppression after pulpectomy with preoperative flurbiprofen. *Journal of Endodontics* **13**, 339–47.
- Flower RJ, Vane JR (1972) Inhibition of prostaglandin synthetase in brain explains the anti-pyretic activity of paracetamol (4-acetamidophenol). *Nature* **240**, 410–1.
- Harrison JW, Gaumgartner JC, Svec TA (1983) Incidence of pain associated with clinical factors during and after root canal therapy. Part 1. Interappointment pain. *Journal of Endodontics* **9**, 384–7.
- Hasselgren G, Reit C (1989) Emergency pulpotomy: pain relieving effect with and without the use of sedative dressings. *Journal of Endodontics* **15**, 254–6.
- Hunskar S, Fasmer OB, Hole K (1985) Acetylsalicylic acid, paracetamol and morphine inhibit behavioral responses to intrathecally administered substance P or capsaicin. *Life Sciences* **37**, 1835–41.
- Hyllested M, Jones S, Pedersen JL, Kehlet H (2002) Comparative effect of paracetamol, NSAIDs or their combination in postoperative pain management: a qualitative review. *British Journal of Anaesthesiology* **88**, 199–214.
- Johnsen DC, Harshbarger J, Rymer HD (1983) Quantitative assessment of neural development in human premolars. *Anatomical Records* **205**, 421–9.
- Katz J, Melzack R (1999) Measurement of pain. *Surgical Clinics of North America* **79**, 231–52.
- Laska E, Siegel, C, Sunshine, A (1991) Onset and duration: measurement and analysis. In: Max M, Portenoy RK, Laska EM, eds. *Advances in Pain Research and Therapy*. New York: Raven Press, pp. 691–8.
- Lesko SM, Mitchell AA (1995) An assessment of the safety of pediatric ibuprofen. A practitioner-based randomized clinical trial. *Journal of the American Medical Association* **273**, 929–33.
- Lipton JA, Ship JA, Larach-Robinson D (1993) Estimated prevalence and distribution of reported orofacial pain in the United States. *Journal of the American Dental Association* **124**, 115–21.
- Macfarlane TV, Blinkhorn AS, Davies RM, Kincey J, Worthington HV (2002) Association between female hormonal factors and oro-facial pain: study in the community. *Pain* **97**, 5–10.
- Malamed S (1986) *Clinical Action of Specific Agents Handbook of Local Anesthesia*, 2nd edn. St Louis, MO: Mosby, pp. 42–66.
- Malmberg AB, Yaksh TL (1992) Hyperalgesia mediated by spinal glutamate or substance P receptor blocked by spinal cyclooxygenase inhibition. *Science* **257**, 1276–9.
- Matthews RW, Scully CM, Levers BG (1984) The efficacy of diclofenac sodium (Voltarol) with and without paracetamol in the control of post-surgical dental pain. *British Dental Journal* **157**, 357–9.
- Muth-Selbach US, Tegeder I, Brune K, Geisslinger G (1999) Acetaminophen inhibits spinal prostaglandin E2 release after peripheral noxious stimulation. *Anesthesiology* **91**, 231–9.
- Oguntebi BR, DeSchepper EJ, Taylor TS, White CL, Pink FE (1992) Postoperative pain incidence related to the type of

- emergency treatment of symptomatic pulpitis. *Oral Surgery Oral Medicine and Oral Pathology* **73**, 479–83.
- O'Keefe EM (1976) Pain in endodontic therapy: preliminary study. *Journal of Endodontics* **2**, 315–9.
- Penniston SG, Hargreaves KM (1996) Evaluation of periapical injection of Ketorolac for management of endodontic pain. *Journal of Endodontics* **22**, 55–9.
- Piletta P, Porchet HC, Dayer P (1991) Central analgesic effect of acetaminophen but not of aspirin. *Clinical Pharmacology and Therapeutics* **49**, 350–4.
- Pogge R (1963) The toxic placebo, I: side and toxic effects reported during the administration of placebo medicine. *Medical Times* **91**, 1–6.
- Reddy SA, Hicks ML (1998) Apical extrusion of debris using two hand and two rotary instrumentation techniques. *Journal of Endodontics* **24**, 180–3.
- Rogers MJ, Johnson BR, Remeikis NA, BeGole EA (1999) Comparison of effect of intracanal use of ketorolac tromethamine and dexamethasone with oral ibuprofen on post-treatment endodontic pain. *Journal of Endodontics* **25**, 381–4.
- Ruiz-Hubard EE, Gutmann JL, Wagner MJ (1987) A quantitative assessment of canal debris forced periapically during root canal instrumentation using two different techniques. *Journal of Endodontics* **13**, 554–8.
- Schwartz D, Lellouch J (1967) Explanatory and pragmatic attitudes in therapeutical trials. *Journal of Chronic Diseases* **20**, 637–48.
- Unruh AM (1996) Gender variations in clinical pain experience. *Pain* **65**, 123–67.