DOSE RESPONSE OF IBUPROFEN COMPARED TO PLACEBO ON POST-SEPARATOR PLACEMENT PAIN

By

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To my husband, Lane for his unending support and encouragement

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LIST OF ABBREVIATIONS

IBU 0	placebo
IBU 200	200 mg ibuprofen
IBU 400	400 mg ibuprofen
IDS	investigational drug service
IL-1B	interleukin 1-beta
NSAID	non steroidal anti-inflammatory drug
PGE_2	prostaglandin E_2
SP	substance P
s.d.	standard deviation
VAS	visual analog scale

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Patients have long associated pain with dental work and orthodontics is no exception to this. With pain being a major drawback to orthodontic treatment, pain control is an increasingly important area for clinicians. The aims of this study were to investigate the efficacy and appropriate dosage of NSAIDs, specifically ibuprofen, as an analgesic for orthodontic pain control using orthodontic separators as a pain model, and also to assess the contribution of gender to the pain experience. Twenty subjects (13 female, 7 male) initiated the study to randomly receive one of three treatments: 400 mg ibuprofen, 200 mg ibuprofen or placebo. The dosing times were one hour prior to separator placement and every six hours thereafter for three days post separator placement. Prior to the first separator placement, a Chewing Efficiency Test and Visual Analog Scales (VAS) for pain experienced with the Chewing Efficiency Test and expected pain with separators were recorded in a pain diary. After the separators were placed, VAS for pain experienced upon placement and pain experienced after placement were completed and recorded in a pain diary which was kept for seven days. Subjects returned to the clinic after one week for separator removal. The subjects returned twice, separated by monthly intervals, to receive a different treatment drug with

the same protocol. Out of the 20 subjects who initiated the study, 13 subjects (7 female, 6 male) completed the study and 7 subjects (6 female, 1 male) withdrew. By the end of the study, the 13 subjects who successfully completed the study received all three treatments medications. Out of the 7 subjects that withdrew; 1 received two treatment medications and 6 received one treatment medication. Based on the mixed model analyses ($p < 0.05$), orthodontic pain relief after separator placement was significant and greatest for the 400 mg dosage of ibuprofen compared to 200 mg of ibuprofen and placebo. No significant differences were detected between genders.

CHAPTER 1
INTRODUCTION

Pain is among the most cited negative effects of orthodontic treatment and is a major concern to patients.[1,2] Orthodontic therapy is reported to be painful for 90% of patients, with some 30% contemplating terminating their treatment early because of discomfort.[3] With this in mind, pain control is an area of interest for clinicians.

Ibuprofen is a common over the counter non-steroidal anti-inflammatory drug (NSAID) that is regularly taken by patients with pain. An NSAID such as ibuprofen has been found to be effective in reducing postoperative pain when pain is a result of tissue damage and inflammation.[4] One study comparing the effect of preoperative vs. postoperative ibuprofen therapy on orthodontic pain revealed that preoperative ibuprofen decreased pain that was experienced 2 hours after separator placement and at bedtime.[5] Also, patients who had taken both preoperative and postoperative ibuprofen doses had lower pain scores altogether. A second study by Law et al.[6] found similar results that revealed patients who took ibuprofen preoperatively had significantly less pain while chewing 2 hours after treatment than did patients who took ibuprofen postoperatively or placebo. While these studies identified ibuprofen as being effective in reducing postoperative orthodontic pain, they did not address the appropriate dosage of ibuprofen to prescribe orthodontic patients seeking pain relief.

Patients who consume ibuprofen for pain relief have the potential of developing negative side affects including gastrointestinal intolerance [6] and inhibition of tooth movement.[6,7] Therefore it would be important to know the appropriate dosage of ibuprofen necessary to alleviate orthodontic pain.

The purpose of this study was to investigate the efficacy of two dosage regimens of ibuprofen (200 or 400 mg three times per day for three days) compared to placebo to determine which treatment regimen is most effective in controlling orthodontic pain over a seven day period using orthodontic separators as a pain model. In addition, potential gender differences were evaluated.

CHAPTER 2
MATERIALS AND METHODS

Sample Population

Twenty non-orthodontic subjects (7 male, 13 female) presented to the University of Florida Orthodontic Clinic for initiation of the study. Prior to separator placement, each subject had to meet the following inclusion criteria:

Inclusion and Exclusion Criteria

- The subject must be between the ages of 18 – 30.
- The subject must not be pregnant.
- If the subject is a female of child-bearing potential, she must consent to a pregnancy test.
- The subject must have second premolars, first molars, and second molars that are in contact, therefore requiring the placement of two separators in each of four quadrants.
- The subject must not be currently taking any steroidal or non-steroidal pain medications or any other anti-pain drugs.
- The subject must have no contraindications or adverse reactions to ibuprofen.
- The subject must have no contraindications or adverse reactions to nuts.
- The subject must give written informed consent for participation in the study.
- The subject must not need antibiotic prophylaxis prior to dental treatment.

Pain Model

Two elastic separators were placed in each quadrant to induce pain. As shown in Figure 2-1, each subject was to randomly receive one of three possible treatment medications one week per month over a three month time span: 200 mg ibuprofen, 400 mg ibuprofen, or placebo. Twenty subjects were recruited to initiate the study while only 13 subjects successfully completed the study.

One hour prior to separator placement, each subject was administered their specific randomized treatment medication. After separator placement, subjects self administered the treatment medication for the first three days, every six hours (three times a day), with food (or at mealtime). The subjects were contacted via a phone call 10 minutes before each dosing time reminding them to take their medication. The dosing times were as follows:

- D1 = drug one hour prior to separator placement
- D2 – D9 = drug every 6 hours (tid) after separator placement for 3 days (Day 1 – Day 3). (Table 2-1)

The Investigational Drug Service (IDS) at Shands Hospital Pharmacy formulated all of the treatment medications to ensure a double-blind research design. The IDS re-encapsulated each treatment medication into two capsules for each dosing time point. The IDS dispensed the tablets to the researcher; the capsules were then dispensed to the subject accordingly and the subject took both capsules at each dosing time point. The order of the treatment medications was randomized per round.

Prior to time of separator placement (Tx), the following instruments were completed by all subjects:

Magnitude Estimations:[8] subjects were asked to identify mild, moderate and intense pain ranges using a 100 mm Visual Analog Scale (VAS) with anchors of “no pain at all” (0mm) and “worst pain imaginable” (100 mm).[9]

Assessment of Expected Pain: subjects were asked to rate their expectation of pain as a result of separator placement prior to separator placement using a 100 mm Visual Analog Scale.

Chewing Efficiency Test[10]*:* each subject chewed a single bagged almond five times on the right side of the mouth without swallowing. This was repeated on the left side of the mouth with another bagged almond. Subjects then rated their pain as a consequence of chewing the almond on a VAS for both right and left sides.

Pregnancy test for all female subjects. The results of the pregnancy test had to be negative for the subject to continue as a participant in this study.

Separators were placed after administration of the above tests (T0) and one hour after the first drug dosing (D1). Two separators (Orthotec, P/N 480302) were placed in each quadrant mesial and distal to the 1st molar. Each separator was placed under the contact for all subjects. Pain upon separator placement was recorded on the VAS in their pain diary. Subjects recorded their pain intensity while chewing, biting and fitting their back teeth together on a VAS in the pain diary at 3 hours post separator placement (T1), 6 hours post separator placement (T2), at bedtime after separator placement (T3), and upon awakening and bedtime (Day 2 - Day 7, T4-T15) (Table 2-1).

To complete the chewing efficiency test and the associated pain recordings, the subjects were given bagged almonds separated for each time point and enclosed in a standard dental sterilization pouch for transport. At bedtime (T3, T5, T7, T9, T11, T13, T15), after the chewing, biting and fitting back teeth together VAS pain scales were completed, each subject self administered the chewing efficiency test by chewing a bagged almond and assessing pain using a VAS located within the pain diary. Each subject returned the completed pain diary and the chewed bags of almonds to the next appointment, one week later, at which time separators were removed.

One investigator (K.M.) measured the VAS ratings and recorded the data for statistical analysis. A calibration procedure of the investigator was conducted prior to all measurements. The calibration was as follows: 10 subjects' Day 2 VAS were measured, then re-measured twice more for a total of three separate measurements. These measurements were carried out over a three week period, with each measurement being separated by one week. Measurements were made using an electronic caliper with an accuracy of 0.01 mm.

Analysis of the chewed almonds was as follows: the whole sample was weighed, the sample was then sifted using a 1 mm^2 mesh, and the separated sample was then weighed. The chewing efficiency was determined to be the percent of the original sample that passed through the sieve. This process was measured in duplicate, and the values averaged for accuracy.

One month later the subjects returned to the clinic to receive a different treatment drug with the same dosing and assessment protocol. After completing the second treatment regimen, the subjects returned one month later to complete the third and final treatment regimen with the same dosing and assessment protocol. At the end of the three months, each subject who successfully completed the study received all three treatment medications. The medical history was updated and eligibility via inclusion and exclusion criteria was confirmed at each visit.

Statistical Analysis

Demographic variables including race, age, sex, height and weight were recorded for each participant at each period and summarized using descriptive statistics.

A linear mixed modeling approach was used to assess differences between treatment groups for the outcomes of interest. Mixed models are able to account for the

structure of the data, with multiple observations over time within each subject, and multiple treatments per subject. A first-order autoregressive correlation structure was used to address the repeated pain measures over the course of a treatment. This allows time points closer in time to be more highly correlated.

Initial models include drug, day number, baseline value (if applicable), period, carryover and drug x day number interaction. Differences by day number between drugs were assessed using a model that included the interaction terms, drug x day number. Carryover effects and period effects were also analyzed in the initial models. A carryover effect is an effect from the previous round influencing the subject during the present round, regardless of what treatment medication the subject was currently receiving. A period effect would be if the pain decreased over periods, regardless of the treatment medication the subjects received or were receiving. If period and carryover effects were not significant, they were removed from the model. For all treatment comparisons, p-values are based on mixed model results, unless otherwise noted, and a p-value of less that 0.05 is considered statistically significant.

As described previously, each subject was asked to indicate mild, moderate and intense pain ranges on a 100 mm VAS. This was conducted at the initiation of each round of the study for each subject. The VAS pain rating data for each round were then standardized to that round's particular magnitude estimations that had been completed at the initiation of the round. For example, a participant may have indicated that the cut point between mild and moderate pain was 20, and the cut point between moderate and intense pain was 60. Then if the subject rated subsequent pain as 60, this would be standardized to 66.7. Similarly, a score of 40 would be standardized as 50.

Table 2-1. Day 1: Treatment and dosing timeline for all subjects to be repeated three times at monthly intervals.

To	D1	Tx	T1	D2	T2	D3	T3
Record height/ weight, Magnitude Estimations, Expected Pain Rating, Chewing Efficiency and Experienced Pain Rating	400 mg ibuprofen	Experienced Pain Rating (VAS)	Pain Diary (Sensory VAS scoring)	400 mg ibuprofen	Pain Diary (Sensory VAS scoring)	400 mg ibuprofen	Pain Diary, Chewing Efficiency and Experienced pain
	200 mg ibuprofen			200 mg ibuprofen		200 mg ibuprofen	
	Placebo			Placebo		Placebo	
-1 hr	-1 hr	Separator Placement	+3 hr	+6 hr	+6 hr	+12 hr	Bed Time

CHAPTER 3
RESULTS

The study sample consisted of 13 females (65%) and 7 males (35%). The race, sex, age, height and weight demographic statistics are described in tables 3-1 and 3-2. Out of the 20 subjects who initiated the study, 13 subjects (7 female, 6 male) completed the study. Data from these subjects were analyzed and included in the results, along with data from the 7 subjects (6 female, 1 male) that withdrew from the study. Withdrawal did not differ by sex (Fisher exact test, p=0.33). By the end of the study, 13 of the 20 subjects received all three treatment medications, 1 received two treatment medications, and six received one treatment medication.

Baseline characteristics by treatment group for expected pain prior to separator placement, almond chewing pain prior to separator placement, chewing efficiencies prior to separator placement and experienced pain at separator placement are listed in Table 3-3. No statistically significant differences were found between treatment groups in standardized expected pain prior to separator placement ($p = 0.52$), between the treatment groups in standardized VAS almond pain scores prior to separator placement ($p = 0.72$) or between the treatment groups in standardized chewing efficiencies prior to separator placement ($p = 0.805$). No statistically significant differences were found between placebo and 200 mg ibuprofen ($p = 0.10$) or 200 mg ibuprofen and 400 mg ibuprofen ($p = 0.09$) when assessing standardized pain at the time of separator placement. However, a statistically significant difference was found between placebo and 400 mg ibuprofen ($p = 0.0017$) treatment groups when assessing standardized pain at the time of separator placement.

In Figure 3-1, Day 0 AM represents the time point three hours after separator placement and Day 7 AM represents the time point at which separators were removed. The time point three hours after separator placement was chosen as Day 0 AM since it was the first time point that included all of the VAS pain ratings (chewing, biting and fitting back teeth together). As shown in Figure 3-1, subjects reported statistically lower levels of pain while taking 400 mg ibuprofen compared to placebo for the three days prescribed. This statistically significant difference is also seen for the remaining days of the week (except Day 4, PM and Day 5, AM), after the treatment medication had been stopped. Also a statistically significant difference in pain levels between 200mg and 400mg ibuprofen is shown at Day 1, Day 2 AM, Day 4 AM and Day 6. In comparison of the placebo and 200mg ibuprofen treatment medications, the only statistically significant differences noted in pain levels were at Day 0 PM and Day 2 PM. Subjects reported having higher mean pain scores for these two treatment groups compared to the 400mg ibuprofen treatment group.

Differences were also noted in reported pain based on the time of day. For all three treatment medications, subjects reported having higher mean pain scores in the evening (PM) versus the morning (AM) through the three days of dosing. Mixed model estimates indicate the standardized pain score is approximately 8 points lower in the morning (coefficient estimate -7,80, s.d. 2.66, p=0.0034). Mean pain appears to peak in the placebo group around the second day of dosing, then shows a progressive decrease for each time point until separators are removed at Day 7 AM.

The VAS almond pain scores are shown in Figure 3-2. Day 0 represents day of separator placement, Day 7 represents day of separator removal. Subjects reported the

least amount of mean pain when chewing the almond while taking 400mg ibuprofen. A statistically significant difference in almond chewing pain levels between placebo and 400mg ibuprofen is seen at Days 0-3 and Day 7. A statistically significant difference in almond chewing pain levels is also seen between 200mg ibuprofen and 400mg ibuprofen at Days 1 and 6; and between placebo and 200mg ibuprofen at Day 0.

Chewing efficiencies are shown in Figure 3-3, with Day 0 representing day of separator placement and Day 7 representing day of separator removal. As shown in Figure 3-3, no treatment medication was found to correlate with a statistically significant higher chewing efficiency. Therefore, chewing efficiency results did not correlate with treatment medication/pain results.

No statistically significant differences were found between gender (p=0.87) for the VAS pain ratings or chewing efficiencies. There was also no evidence of a carryover (p=0.95) or period (p=0.48) effect.

Table 3-1. Race and gender demographics

	Frequency	Percentage
Female	13	65
Male	7	35
White	13	65
Black	1	5
Hispanic	2	10
Asian	2	10
Other	2	10

Table 3-2. Descriptive statistical variables

	Median	Mean	Std Dev
Age (yrs)	27.2	27.1	3.1
Height (in)	67.0	66.2	3.2
Weight (lbs)	140.0	143.1	22.5

Table 3-3. Baseline characteristics by treatment group

Treatment	Variable	Mean	Lower 95% Confidence Level for Mean	Upper 95% Confidence Level for Mean
IBU 0	Expected prior	39.59	24.21	54.97
	Chew prior	3.61	0.76	6.45
	Chew Efficiency prior	49.50	37.34	61.66
	Experienced	52.51	42.50	62.53
IBU 200	Expected prior	42.39	31.10	53.69
	Chew prior	5.40	0.25	10.56
	Chew Efficiency prior	46.33	33.33	59.34
	Experienced	43.09	34.42	51.76
IBU 400	Expected prior	35.55	26.46	44.64
	Chew prior	2.88	1.59	4.18
	Chew Efficiency prior	45.83	33.37	58.30
	Experienced	35.42	24.33	46.50

p-value	Variable	IBU 0 vs IBU 200	IBU 200 vs IBU 400	IBU 0 vs IBU 400
0.52	Expected prior			
0.72	Chew prior			
0.805	Chew Efficiency prior			
0.0064 *	Experienced	0.10	0.09	0.0017 *

Expected prior = VAS expected pain prior to separator placement
Chew prior = VAS almond chewing pain prior to separator placement
Chew Efficiency prior = Chewing efficiency prior to separator placement
Experienced = Experienced pain at separator placement
* = $p < 0.05$ (statistical significance)

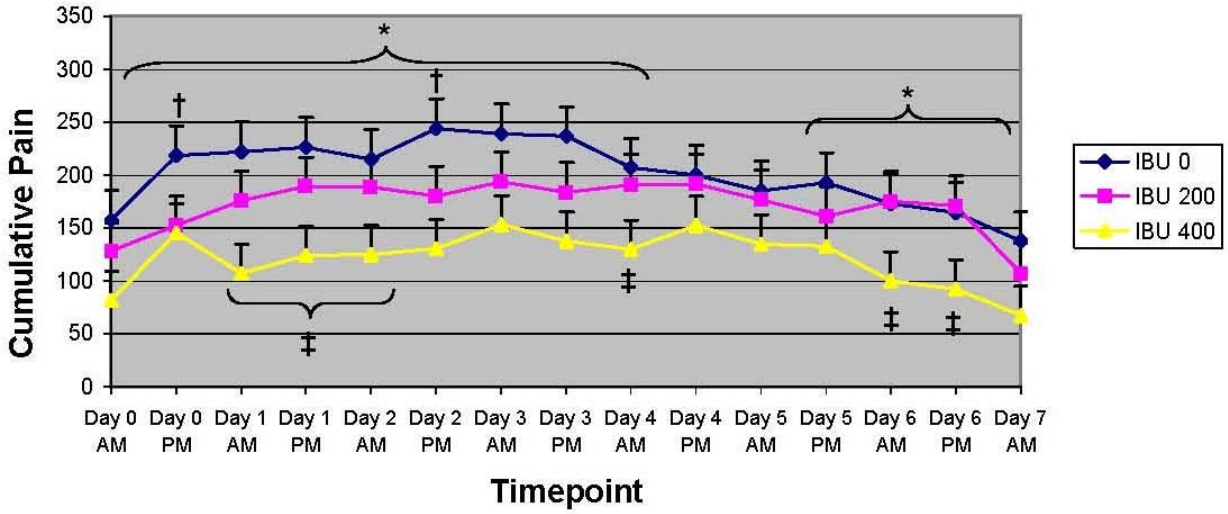

Figure 3-1. Mean cumulative VAS pain scores for all treatment medications at each time point. † = $p < 0.05$ for IBU 0 vs. IBU 200. * = $p < 0.05$ for IBU 0 vs IBU 400. ‡ = $p < 0.05$ for IBU 200 vs IBU 400.

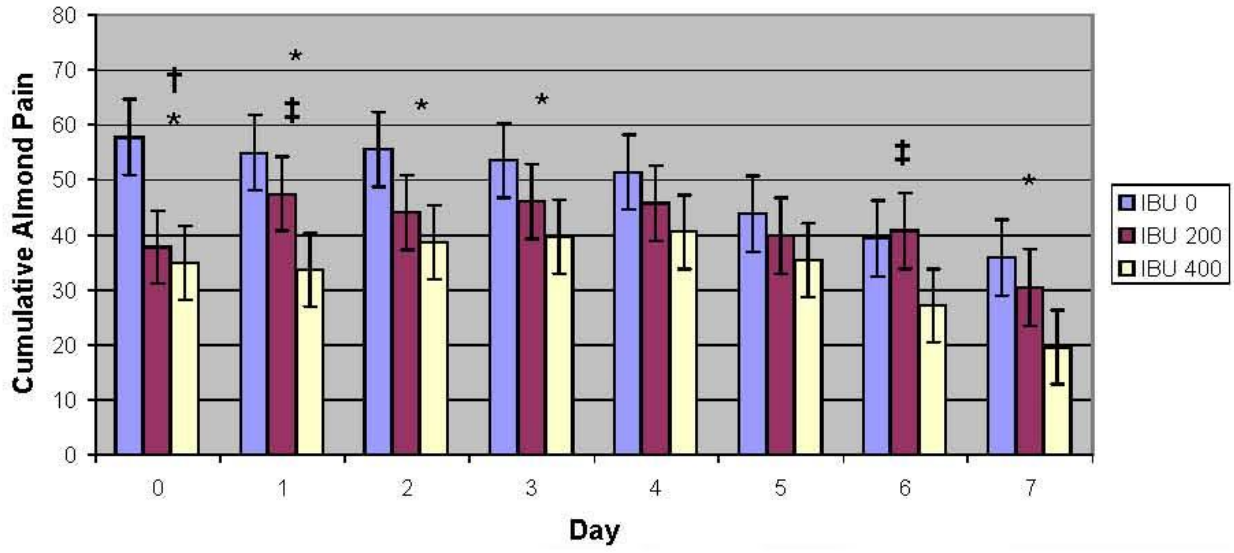

Figure 3-2. Mean cumulative VAS almond pain scores for all treatment medications at each time point. † = $p < 0.05$ for IBU 0 vs. IBU 200. * = $p < 0.05$ for IBU 0 vs. IBU 400. ‡ = $p < 0.05$ for IBU 200 vs. IBU 400.

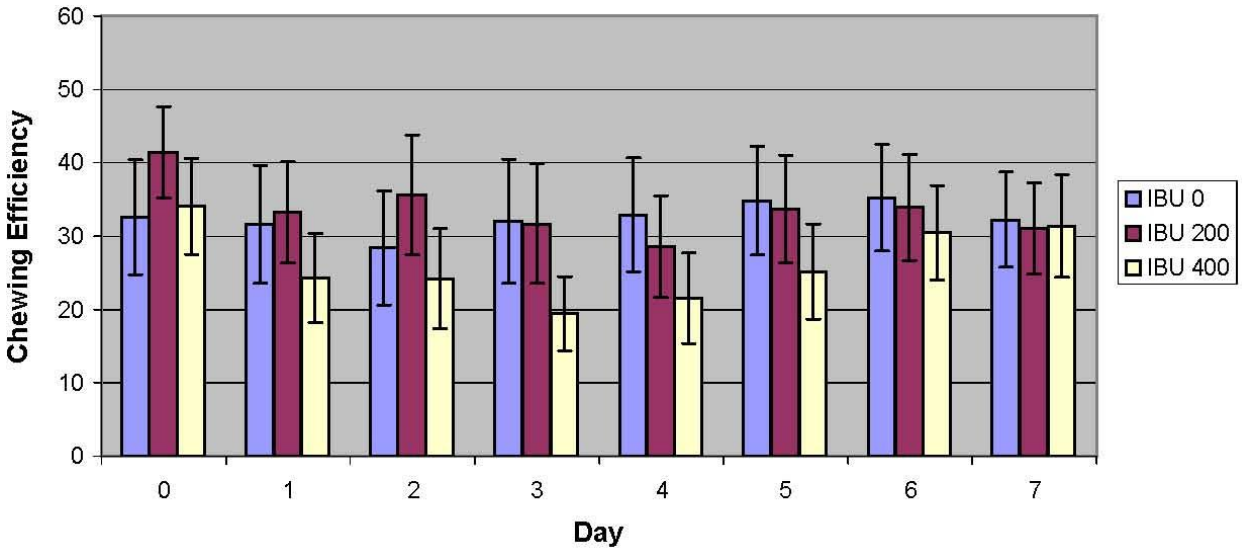

Figure 3-3. Mean chewing efficiency scores for all treatment medications at each time point. No statistically significant differences among groups was identified ($p > 0.05$).

CHAPTER 4
DISCUSSION

As stated previously, pain is a major concern for patients considering orthodontic treatment. One survey rated pain as the greatest dislike during treatment and fourth among major fears and apprehensions prior to orthodontic treatment.[11]

This study was designed as a prospective, double blind, complete block crossover clinical trial that compared the efficacy of two different doses of ibuprofen or placebo in reducing the incidence and severity of orthodontic pain. Ibuprofen was selected as the drug of choice after reviewing several articles that investigated ibuprofen versus other over the counter analgesics. One study compared ibuprofen to aspirin and placebo in controlling orthodontic pain after initial archwire or separator placement and found that the ibuprofen group perceived significantly less discomfort than did the aspirin group and concluded that ibuprofen is the preferred analgesic in the treatment of pain associated with orthodontic adjustments.[12] A second study investigated ibuprofen, acetaminophen, naproxen sodium and placebo on pain experienced with orthodontic separators. The investigators found that ibuprofen given 1 hr prior to separator placement, and 3 and 7 hrs following placement, reduces post-separator placement pain compared with placebo, and that naproxen sodium and acetaminophen do not significantly differ from placebo.[13] Since ibuprofen has been identified as the drug of choice in treating orthodontic pain, the current study was conducted to identify the specific dosage and schedule of ibuprofen

that is necessary to prescribe orthodontic patients in treatment of orthodontic pain.

As stated previously, twenty subjects initiated the current study while only 13 subjects successfully completed the study. The 7 subjects that did not complete the study cited pain as being the reason for dropping out. Out of these 7 subjects, 6 were female and 1 was male. From these results it would appear that females were more likely to withdraw from the study compared to males, but as reported earlier this was not the case since withdrawal did not differ by sex (Fisher exact test, $p=0.33$). The fact that females make up 65% of the initial study sample could explain the female withdrawal trend noted; more females would be expected to withdraw since more females initiated the study. The data analyzed included the 13 subjects who completed the study and the 7 subjects who withdrew from the study.

Based on the results, pain relief following separator placement was significantly related to the treatment medication. When dosed with 400 mg ibuprofen one hour prior to separator placement, subjects reported a statistically greater pain relief at immediate time of separator placement versus placebo. Subjects also reported the greatest mean pain relief after separator placement while taking 400 mg ibuprofen every six hours after a meal. While in some patients 200 mg ibuprofen might be adequate, it would be difficult to determine which patients this would include. To extrapolate this information to our clinical practice, practitioners have two choices of treatment for reduction of orthodontic pain experienced after each appointment. Practitioners could start by prescribing

patients 200 mg ibuprofen three times a day for three days for orthodontic pain relief, then increase the dosage to 400 mg ibuprofen three times a day for those patients who need greater pain relief. Another option would be to prescribe patients 400 mg ibuprofen three times a day for three days for orthodontic pain relief if a 400 mg dose of ibuprofen is not contraindicated due to a medical history that would prohibit prescribing aspirin or NSAIDS.

Another finding from this study is the difference in pain reported by subjects based on the time of day. Subjects reported generally more pain in the evening than in the morning through the three days of dosing for all three treatment medications. Pain has been found to exhibit a pattern, with evening and nights showing the highest scores of pain.[14] One study proposed that the mechanism of pain involves an inflammatory response as a result of tissue damage, rather than a compressive force, which would presumably result in greater pain levels immediately after the separator placement appointment.[6] This diurnal variation could be explained by a natural progression of pain after a traumatic experience like separator placement, which initiates an inflammatory response.

There is no doubt that orthodontic pain is part of an inflammatory reaction causing changes in blood flow following orthodontic tooth movement.[15] The inflammation caused by orthodontic force application stimulates the release of various biochemical mediators such as substance P, histamine, enkephalin, dopamine, serotonin, glycine, glutamate gamma-amino butyric acid, prostaglandins, leukotrienes and cytokines.[15] Inflammatory mediators such as interleukin 1B (IL-1B), substance P (SP), and prostaglandin E_2 (PGE_2) increase

significantly during inflammation. Prostaglandins enhance the transmission of painful stimuli and have been shown to cause hyperalgesia; in explanation prostaglandins sensitize the peripheral pain receptors to send a pain signal to the central nervous system (CNS). One study examined the presence of these inflammatory mediators in gingival crevicular fluid after the placement of separators.[16] After day 1, all 3 substances increased to the highest percentage at treatment sites of all tested occasions versus the controls. This shows that IL-1B, SP and PGE_2 were expressed during initial tooth movement in sufficient amounts. Another study of the same sample examined the gingival crevicular fluid of the tension versus compression sides of a tooth following separator placement.[17] The authors found that IL-1B, SP and PGE_2 were increased by orthodontic forces that cause bone remodeling/inflammation, and their levels were significantly greater in the tension sites than in the compression sites. These results indicate that the application of mechanical force, even a light force induced by a separator, provokes an inflammatory reaction which is reflected by changes in the gingival crevicular fluid composition. The natural progression of this inflammatory reaction could explain why more pain was reported by subjects in the evening. Since orthodontic appointments occur during the day, pain would tend to peak in the evening, after the inflammatory pathways had time to initiate and proceed.

During the days following an orthodontic appointment the inflammatory response will be proceeding at a constant rate and therefore would not explain the diurnal variation that is noted in this study during the remaining days of the

week. An explanation for the diurnal variation noted throughout the week in this study could be explained by hormonal control of the body. Cortisol is a corticosteroid hormone produced by the cortex of the adrenal gland. Cortisol is referred to as the stress hormone and is involved in response to stress and anxiety, and reduces immune responses (inflammation). Hydrocortisone is a well-known synthetic form of cortisol and is used for its anti-inflammatory effects to treat a variety of conditions, including rheumatoid arthritis. The amount of cortisol in the blood undergoes a diurnal variation – with the highest levels present in the early morning and lowest levels present in the late evening.[18] Cortisol's natural anti-inflammatory effects could be causing the diurnal variation seen in orthodontic pain days after the procedure takes place.

The duration of pain after orthodontic treatment has been initiated has also been investigated. The consensus reported is that pain begins a few hours after initiation of an orthodontic force and lasts approximately 5 – 7 days; after day 5 only mild discomfort was reported by patients. [19,20] Our results seem to agree with this finding. In our study we observed mean pain to peak in the placebo group around Day 2 PM and then progressively decrease until separator removal at Day 7 AM. Our findings also seem to agree with clinically controlled trials by Ngan [12,21] and by Giannopoulou [16] which shows discomfort associated with separator placement, which usually starts within 4 hours after insertion and peaks at 24 hours after insertion, decreases to pre-placement level within 7 days. On the other hand, our findings differed in that observed mean pain peaked around Day 2 PM, not 24 hours after separator placement. Since mean pain

peaks around Day 2 PM, our protocol to administer the treatment medication for only three days post separator placement is justified.

Pain relief following almond chewing was also significantly related to the treatment medication. Subjects reported the greatest mean pain relief while chewing the almond when taking 400mg ibuprofen as prescribed. Also, this finding agrees with the previously mentioned result of subjects reporting the greatest mean pain relief while taking 400 mg ibuprofen as prescribed for orthodontic pain. Therefore, to reduce orthodontic pain experienced during chewing, 400mg ibuprofen should be prescribed. Again, in some patients 200mg of ibuprofen might be adequate but these patients would be difficult to identify. Since no statistically significant differences were found between the treatment groups for VAS almond pain scores prior to separator placement, each treatment medication was determined to be equally effective in treating almond chewing pain prior to separator placement.

No correlation was noted between chewing efficiencies and treatment medication. Since no statistical significance was found, all treatment medications are treated as being equally effective in leading to good chewing efficiencies. Also, no statistically significant differences were found between the treatment groups for expected pain prior to separator placement. Based on these results there was no evidence of a carryover effect or period effect. As previously described, carryover and period effects may influence the subject's pain perception and therefore scoring of the VAS. In a carryover effect, if the subject experienced what they perceived as a painful experience in the previous round of

the study, that experience could negatively affect the subject in the next round of the study and influence their scoring of the VAS. A period effect would be if pain decreased over periods, regardless of the treatment medication the subjects received. In this study, period 1 = first round of the study with the first treatment medication, period 2 = second round with the second treatment medication, and period 3 = third round with the third treatment medication. After evaluation of the data, these effects were found to not be a factor in influencing the subjects in any way.

Pain perception can be dependent upon variables such as age, gender, individual pain threshold, the magnitude and duration of the force applied, present emotional state and stress, cultural differences and previous pain experiences.[21,22] Traditionally, it is believed that females are “fragile” and sensitive to pain, while males are more stoic and can tolerate more pain.[23] Conflicting results have been reported with some showing that males are more willing to tolerate pain than females, but others report no differences between males and females in reporting the feeling of pain with respect to threshold.[24] Scheurer et al.[25] found significant differences in response of pain between the sexes. Girls reported significantly greater pain intensity and consumed significantly more analgesics than males. In contradiction to this, Jones et al.,[26] and Erdinc et al.[27] both reported no significant differences between sexes in perception of pain during orthodontic treatment. Likewise, the current study did not detect any statistical differences found in pain perception based on gender differences.

As stated previously, ibuprofen was selected as the drug of choice after several studies identified it as being the best over the counter analgesic to successfully treat orthodontic pain.[5,12,13] The drawbacks to ibuprofen therapy in controlling orthodontic pain are the possible side effects and potential to inhibit tooth movement. The most common side effect of ibuprofen is gastrointestinal intolerance. It has been reported that gastrointestinal side effects occur in up to 15% of patients taking ibuprofen.[6] Ibuprofen also reversibly alters platelet function and prolongs bleeding time. These side effects could be significant if multiple doses are taken by the patient over an extended time period. That is why in this study, the subjects were prescribed over the counter doses and not an amount that would be prescribed for a clinical condition or that may exceed the clinically recommended limit.

As described previously, when adequate mechanical forces are applied to teeth, an acute inflammatory response occurs in the periodontal tissues and many inflammatory mediators are released, including prostaglandins (more specifically PGE_2). Prostaglandins are thought to be mediators of tooth movement by altering the activity or the numbers of osteoclasts or osteoclast-like cells.[17,28] Since NSAIDs like Ibuprofen are inhibitors of prostaglandins, it is reasonable to expect that they would inhibit or delay orthodontic tooth movement.[6,7] Administering 2400-3200mg ibuprofen for 2 weeks will reach anti-inflammatory levels. In the current study, we administered at the most 1200 mg/day for three days. Therefore in this study, drug levels did not reach the anti-inflammatory levels and therefore should not inhibit tooth movement.

Since ibuprofen serum levels do not reach anti-inflammatory levels, the analgesic effects of ibuprofen are largely due to a central-acting mechanism of action. One study showed that spinal administration of NSAIDs block hyperalgesia induced by the activation of spinal glutamate receptors.[29] Another study which administered N methyl D aspartate (NMDA) to invoke a centrally acting hyperalgesia in rats (biting, scratching, licking) showed that this pain response was reduced when ibuprofen was administered intra-peritoneally. NMDA is an excitatory amino acid receptor agonist in the CNS.[30] Ibuprofen in this study was shown to reduce the peak response and duration of the centrally acting hyperalgesia response elicited by NMDA injections. These findings demonstrate that the analgesic effects of NSAIDs can be dissociated from their anti-inflammatory actions.

When determining statistical power, an important point to consider is study design. Previous studies on managing orthodontic pain with analgesics have been parallel arm, in which each subject receives only one treatment. The current study was designed to be a complete block crossover design, with all subjects receiving all three of the possible treatments. However, not all subjects successfully completed the study, but their data was included. While not all participants completed the study, most received more than one treatment medication, which still has better statistical power than a parallel arm study. With the incomplete block study design, much of the between-subject variability can be eliminated since most of the subjects received all three treatment medications.

There are limitations to this study. We experienced a high drop-out rate for subjects which led to a small sample size. Based on estimates from our data for standardized VAS pain scores, and assuming 13 subjects with complete information, we had 0.80 power (two-sided test, level of significance 0.05, s.d. 90 for within subject drug differences) to detect a difference of 76 between two drug doses. In a similar parallel arm study (s.d. 109 for each dose, based on estimates from our data), 68 subjects would be required to duplicate the power and detectable difference of our study. Also, each subject's raw data for each round was normalized to their magnitude estimation ratings for that specific round, which minimized within and between-subject variability. The inclusion of data from one subject who required rescue medication during one round of the study is another limitation. Subjects were to contact the Principal Investigator if rescue medication was needed, and the rescue medication prescribed was 650 mg acetaminophen. Another potential limitation is non compliance with the protocol. Even though subjects received a reminder phone call to self administer their medication, they may not have self-administered on time. Also, subjects eat meals at different times and go to bed at different times, therefore complete the pain diary at different times which could affect pain scores. The age range of subjects in this study was between 18 - 30 years, but many individuals receiving orthodontics are younger. While there is no reason to think that the current information cannot be applied to other age groups, those studies need to be done for confirmation.

CHAPTER 5
CONCLUSIONS

Previous studies investigating pain relief following orthodontic appointments identified ibuprofen as being the analgesic of choice, but did not identify the proper dosing schedule of ibuprofen to be prescribed to orthodontic patients. In this study, 400 mg ibuprofen administered one hour prior to orthodontic appointments and subsequently three times a day for three days after orthodontic appointments was found to statistically reduce pain from chewing, biting and fitting back teeth together in an orthodontic tooth separator model compared to 200 mg ibuprofen and placebo. From these findings, 400 mg ibuprofen administered one hour prior to orthodontic appointments and subsequently three times a day for three days after orthodontic appointments is suggested as the appropriate dosing schedule to be prescribed to patients seeking orthodontic pain relief.

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BIOGRAPHICAL SKETCH

Katherine B. Miller received her Bachelor of Science in zoology from Auburn University in Auburn, Alabama in 2001. She continued her education at the University of Alabama Birmingham College of Dentistry in Birmingham, Alabama and earned her Doctor of Dental Medicine in 2007. Upon completion of her dental training, she continued her education at the University of Florida College of Dentistry in Gainesville, Florida earning a Master of Science with a certificate in orthodontics in 2010.