EFFECTS OF PREOPERATIVE IBUPROFEN, ANXIETY, AND GENDER ON POST-SEPARATOR PLACEMENT PAIN

By

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Many patients experience pain with orthodontics. However, there is no widely accepted standard of care for controlling orthodontic pain. Previous studies have been inconclusive as to the most effective way to manage orthodontic pain. The purpose of this study was to assess the effectiveness of preemptive ibuprofen added to an ibuprofen regimen administered after separator placement in reducing pain. The study also assessed contributions of psychological factors and gender to pain. Subjects were randomly assigned to Group A: 400 mg ibuprofen 1 hour before separator placement (D1), 3 hours after placement (D2) and 7 hours after placement (D3); Group B: placebo at D1, 400 mg ibuprofen at D2 and D3; or Group C: placebo at D1, D2, and D3. Prior to separator placement, subjects completed two psychological surveys, a Masticatory Efficiency Test, and a Visual Analog Scale for expected pain and experienced pain during the Masticatory Efficiency Test. After placement, subjects recorded the actual pain experienced, kept a pain diary for 24 hours following separator placement, and

performed a 24-hour follow up Masticatory Efficiency Test. Significantly less pain ($p<0.05$) was experienced at 6 hours, at bedtime, and at time of awakening on the second day when ibuprofen was administered before and after separator placement. Preemptive administration of ibuprofen is recommended to orthodontic patients before separator placement.

CHAPTER 1
INTRODUCTION

A significant number of patients experience moderate to severe pain as a result of initial orthodontic treatment.[1-4] Orthodontic forces cause a disruption of the periodontal tissues initiating a cascade of events involving the release of inflammatory mediators, such as prostaglandins, into the local environment.[5] Nonsteroidal anti-inflammatory drugs (NSAIDs) act by inhibiting cyclooxygenase (COX) enzymes thereby blocking the formation of prostaglandins and preventing both inflammation and the sensitization of peripheral nociceptors.[6] If NSAIDs are given before a procedure, the body may absorb and distribute the medication before tissue injury occurs. This could allow for a decrease in the production of prostaglandins and thus a decrease in the inflammatory response.[7] Prior administration of NSAIDs may also exert an analgesic effect by blocking afferent nerve impulses before they reach the central nervous system.[8]

Several authors have conducted studies evaluating pain following separator or archwire placement. It has been found that pain is present within 4 hours and continues until at least 24 hours dissipating by day 7. [1,9,10] This is in agreement with other studies,[2,3] which have found the greatest need for analgesics to be within 3 days after archwire placement. Bergius et al. [11] found that 87% of participants reported pain on the first evening, but the most intense pain was reported to occur the day after placement. Females reported significantly higher pain during days 3-7 than males.

A limited number of similar studies have focused on orthodontic pain control. Ngan et al.[12] found ibuprofen and aspirin to provide more relief of orthodontic pain than

placebo when one dose was given immediately after separator or archwire placement. They concluded that ibuprofen is the choice analgesic to control orthodontic pain since it produced less pain than aspirin. Law et al.[13] found that subjects who took preemptive ibuprofen reported less pain at 2 hours than subjects who had placebo or ibuprofen after separator placement. However, no significant differences were found between the post-treatment group and the placebo group at any time during the seven days. Bernhardt et al.[14] found that subjects who received ibuprofen before separator placement or pre- and post-treatment ibuprofen were in less pain at 2 hours and at bedtime than subjects who received only post-treatment ibuprofen. No significant differences were found between the pretreatment and combined therapy groups, but there was a trend toward decreasing pain starting on day 2 for the combined therapy group.

Polat et al.[15] evaluated the effects of one preemptive dose of ibuprofen (400mg), naproxen sodium (550mg), or placebo given one hour before archwire placement. Patients taking naproxen sodium had significantly less pain than the ibuprofen or placebo groups at 2 hours, 6 hours, and nighttime. Although the pre-treatment ibuprofen group showed a trend for decreased pain experienced at 2 hours and 6 hours, there were no statistically significant differences between the placebo and ibuprofen groups. Another study by Polat and Karaman[16] compared orthodontic pain control achieved with a preemptive and one post-treatment (6 hours after bonding) dose of 600 mg ibuprofen, 100 mg flurbiprofen, 500 mg acetaminophen, 550 mg naproxen sodium, 300 mg aspirin, or placebo. The results showed that all of the analgesics decreased the pain compared to the placebo group. However, the lowest pain levels were experienced by those taking naproxen sodium, aspirin, and acetaminophen.

Currently, patients are told that separators may cause discomfort in the days following placement. They are instructed to take over-the-counter pain medication as needed for pain. Unfortunately, there is no widely accepted standard of care that is followed for managing orthodontic pain. The intent of this study was to add to the body of knowledge in determining an optimal treatment for controlling pain in orthodontics. The specific purpose was to assess the effectiveness of preemptive ibuprofen added to an ibuprofen regimen administered after separator placement in reducing pain. The study also assessed contributions of psychological factors and gender to pain.

CHAPTER 2
METHODS

This was a double blind, parallel arm, prospective study that was approved by the Institutional Review Board of University of Florida. In order to participate, patients had to meet the following inclusion criteria: 1) at least 13 years of age and not older than 30, 2) females had to consent to a pregnancy test and could not be pregnant, 3) beginning orthodontic treatment for the first time, 4) orthodontic treatment required the placement of at least one separator in each of four quadrants, 5) no contraindications or adverse reactions to ibuprofen or almonds, and 6) must give written informed consent for participation in the study. Subjects were compensated for their participation with a $200 decrease in their orthodontic treatment fee. Fifty-one subjects were randomly assigned to one of three groups stratifying for gender. (Table 2-1) Group A (16 subjects) received 400 mg ibuprofen 1 hour prior to separator placement (D1), 3 hours after separator placement (D2), and 7 hours after separator placement (D3). Group B (17 subjects) received placebo at D1 and 400 mg ibuprofen at D2 and D3. Group C (18 subjects), the control group, received placebo at D1, D2, and D3.

The investigational drug pharmacy at Shands Hospital dispensed the ibuprofen/placebo so that the researcher would be blinded to the treatment group. Two hundred mg caplets of ibuprofen were re-encapsulated and placebos were made to match. Two capsules were taken at each dosing time.

A treatment timeline can be seen in Table 2-1. Prior to time of first dosing (D1), the subjects completed the following:

1) Expectation of pain**:** subjects were asked to rate their expectation of pain consequent to separator placement using a 10 cm Visual Analog Scale (VAS). Anchors of "no pain at all" (0 cm) and "worst pain imaginable" (10 cm) were used.[17]

2) Pre-existing affective state was assessed using the State and Trait Anxiety Inventory (STAI)[18] and the Positive Affect Negative Affect Schedule (PANAS)[19].

3) Modified Mastication Performance Index[20]: subjects were asked to chew a bagged almond five times on the right side of the mouth without swallowing. This was repeated on the left side of the mouth. The protocol was modified from Al-Ali, Heath and Wright, 1999.[20] Subjects were asked to rate pain as a consequence of chewing the almond on a VAS for both right and left sides.

4) If the patient was female and of child-bearing potential (i.e., post-menarche), a pregnancy test was administered at this time. The results of the pregnancy test had to be negative for the patient to continue as a participant in this study.

Table 2-1: Treatment Timeline[a]

T_0	D_1	Tx	T_1	D_2	T_2	D_3	T_3	T_4	T_5
• Expected pain rating • STAI, PANAS • Masticatory Performance Index and Experienced Pain Rating • Pregnancy test for females	Gp A: (n=16) 400mg Ibuprofen Gp B: (n=17) Placebo Gp C: (n=18) Placebo	Experienced Pain Rating	Pain Diary	Gp A: 400mg Ibuprofen Gp B: 400mg Ibuprofen Gp C: Placebo	Pain Diary	Gp A: 400mg Ibuprofen Gp B: 400mg Ibuprofen Gp C: Placebo	Pain Diary	Pain Diary	Masticatory Performance Index , Experienced Pain Rating and Pain Diary
-1.25hr	-1 hr	Separator placement	+2 hr	+3 hr	+6 hr	+7hr	Bed time	Wake up	24 hr

[a] T_0, prior to dosing; Tx, separator placement,; T_1, 2 hours after separator placement; T_2, 6 hours after separator placement; T_3, bedtime; T_4, time of awakening; T_5, 24 hours after separator placement; D_1, time of first dosing; D_2, time of second dosing; D_3, time of third dosing

Separators were placed one hour after the first dosing and administration of the above tests (T0). Ormco posterior separators (P/N 640-0080, Glendora, CA) were placed unless the clinical situation warranted the use of metal separators. At least one separator was placed in each quadrant. The method of placement, either over or under the contact, was recorded for each separator placed. Pain upon placement was recorded on a VAS.

Over the next 24 hours, subjects recorded discomfort when biting, chewing, fitting front teeth together, and fitting back teeth together in a VAS pain diary, similar to that

used in other studies.[1,12-14] Pain scores were recorded in the pain diary at: 2 hours post-separator placement (T1), 6 hours post-separator placement (T2), at bedtime (T3), at time of awakening (T4) and at 24 hours post-separator placement (T5). Subjects provided the specific times for bedtime and awakening in the pain diary. Subjects self-administered the remaining two doses at 3 hours after separator placement (D2) and at 7 hours after separator placement (D3). At 24 hours (T5), subjects self administered the masticatory efficiency test with VAS. The completed pain diary and the chewed bagged almonds were returned to the investigator by mail.

The chewed almond sample was removed from the bag and poured into a 10 mesh sieve. The separated sample was then weighed. Part A was the portion of the original almond weight that was remaining in the sieve and part B was the portion that passed through the sieve. The bite efficiency was defined as % part B.[20]

Two investigators (CM and VM) with the same level of training did all data collection and separator placement. Summary statistics and graphical methods were used to examine the data. Two sample t-tests and analysis of variance were used for baseline and 24 hour comparisons between treatment groups and between sexes. Relationships between pain on placement and expected pain and pain on placement and psychological variables were examined by calculating Pearson correlation coefficients. Linear mixed models were used to examine the VAS pain ratings over time. An auto-regressive correlation structure accounted for correlation within an individual, with pain measures closer in time more highly correlated. The primary analysis outcome was the sum of pain ratings (biting, right and left; chewing, right and left; fitting back teeth together; and fitting front teeth together) at each time point, with secondary analyses done to examine

the separate components of biting, chewing, fitting back teeth together, and fitting front teeth together. Initial models included variables representing the timepoints, treatment group, and timepoint by treatment interaction. The interaction term allows for the pain response pattern to vary over time, depending on treatment group. Contrasts were used to assess treatment differences at each timepoint. The impact of adding additional covariates to our primary model (sex, age, baseline characteristics) was also examined. Akaike's information criterion was used to compare models. For all analyses, a p-value of less than 0.05 was considered statistically significant.

CHAPTER 3
RESULTS

Baseline data (Table 3-1) showed no significant differences between groups for gender, age, STAI, PANAS, expected pain, pain on separator placement, bite efficiency, and pain during the bite efficiency test. Although the groups were stratified for gender, group B ended up with only 41% females while group A had 63% females, and group C had 72% females. However, this was not a statistically significant difference. The state anxiety group averages were 32.6-33.3 (scale of 20-80) and the trait anxiety group averages were 33.9-36.4. The positive affect group averages were 30.4-32.4 (scale of 10-50) while the negative affect group averages were 13.4-15.1. The averages for expected pain on placement, recorded with the VAS were 4.4-4.9 (on a scale of 0-10) while the actual pain experienced was only 2.6-3.5. The average baseline bite efficiency ranged from 19% to 29% while the average baseline pain during this bite test was 0.0-0.5.

Table 3-1: Baseline (T_0) Characteristics- Mean (standard deviation)[b]

	Group A	**Group B**	**Group C**	**p-value**
N	16	17	18	
Gender (%female)	63	41	72	0.16
Age	17.6 (5.0)	14.9 (2.7)	16.4 (3.6)	0.15
State anxiety	33.3 (7.6)	33.3 (8.8)	32.6 (3.6)	0.95
Trait anxiety	36.4 (7.2)	35.1 (7.4)	33.9 (7.3)	0.62
Positive affect	30.8 (6.4)	32.4 (8.9)	30.4 (8.3)	0.74
Negative affect	14.5 (4.4)	15.1 (3.5)	13.4 (3.3)	0.41
VAS expected	4.9 (2.1)	4.7 (1.8)	4.4 (1.4)	0.72
VAS placement	3.1 (2.4)	3.5 (2.9)	2.6 (2.2)	0.59
Bite efficiency R	25 (26)	19 (23)	28 (24)	0.59
Bite efficiency L	29 (31)	26 (28)	28 (25)	0.96
VAS bite R	0.0 (0.0)	0.2 (0.3)	0.1 (0.1)	0.16
VAS bite L	0.0 (0.1)	0.5 (1.5)	0.2 (0.8)	0.43

[b]VAS expected, expectation of pain with separator placement; VAS placement, pain on placement; VAS bite R, pain during bite efficiency test on right side; VAS bite L, pain during bite efficiency test on left side

There were no significant differences between groups A, B, or C for masticatory efficiency index or pain with this test on either day 1 (Table 3-1) or on day 2 at 24 hours (data not shown). There were significant decreases in bite efficiency and significant increases in pain with this test from day 1 to day 2 (data not shown). However, there were no differences between groups.

Males and females were compared for expected pain, pain on separator placement, and the change in pain with the masticatory efficiency test from day 1 to day 2 (Table 3-2). No statistically significant gender differences were found. However, there was a trend for more pain on placement and a greater increase in pain with the 24 hour bite efficiency test for females.

Table 3-2: Gender Comparisons- Mean (standard deviation)[c]

	Males	**Females**	**p-value**
VAS expected	4.3 (1.8)	5.0 (1.7)	0.17
VAS placement	2.4 (2.4)	3.5 (2.5)	0.10
Change in VAS bite R	5.9 (3.2)	7.2 (2.2)	0.09
Change in VAS bite L	5.7 (3.7)	7.1 (2.2)	0.14

[c]VAS expected, expectation of pain with separator placement; VAS placement, pain on placement; Change in VAS bite R, change in pain during bite efficiency test on right from day 1 to day 2; Change in VAS bite L, change in pain during bite efficiency test on left from day 1 to day 2.

Pearson correlation coefficients were calculated for pain on placement compared to expected pain, STAI, and PANAS (Data not shown). No significant relationship was found between the expected pain and actual pain experienced with separator placement. Additionally, no significant correlations between pain on placement and PANAS or STAI were found.

The results from the 24-hour pain diaries can be found in Table 3-3. Results for biting, fitting back teeth together, and for the total pain experienced can be seen in Figures 3-1,3-2, and 3-3. Figures for chewing and fitting front teeth together are not shown but are similar to the others. At 6 hours, Group A (ibuprofen at all 3 dosing times)

experienced significantly less pain than both Groups B and C when biting and less than Group C when chewing and fitting back teeth together. At this timepoint, Group A reported less pain then Group B when fitting front teeth together. Group A was also significantly different from the other two groups for the combined pain of chewing, biting, fitting back teeth together, and fitting front teeth together. At bedtime, the pain recorded by Group A was significantly less than that reported by the other two groups for chewing and biting. Group A had less pain than Group C for fitting back teeth together and less than Group B for fitting front teeth together at this timepoint. Group A also had significantly less combined pain than the other groups at bedtime. By the morning of the second day, Group A only differed from Group C when biting, and there was a rebound effect by 24 hours with a trend for Group A to experience more pain than the other two groups.

The following variables were added to the initial model of the sum of the pain ratings: sex, age, state anxiety, trait anxiety, positive affect, negative affect, VAS for expected pain, and VAS for pain on placement. Both main effect and added variable by treatment group interactions were considered when appropriate. The only added variable that was significant was VAS pain on placement. In the model containing VAS pain on placement, each unit increase in this variable was associated with approximately a 2 unit increase in the summary pain measure. Using this model to evaluate treatment differences by timepoint, the 6 hour difference between groups A and B dropped to marginal significance ($p=0.0514$), as might be expected since group B had a higher mean VAS pain on placement score (3.5) than group A (3.1). Significance of the main effects

for this model are: timepoint, p<0.0001; treatment group, p=0.06; treatment group by time point interaction, p=0.0065; and VAS pain on placement p=0.0017.

Table 3-3: - Pain Diary- Mean VAS scores (standard error)[d]

	Timepoint	**Group A**	**Group B**	**Group C**	**Significance**
Chewing	2 hrs	3.6 (1.2)	5.9 (1.4)	4.8 (1.0)	
(Sum of R/L)	6 hrs	4.1 (1.3)	7.2 (1.3)	8.5 (1.3)	A < C
	Bedtime	3.0 (0.6)	7.3 (1.3)	9.9 (1.3)	A < B, C
	Awakening	7.3 (1.4)	9.2 (1.5)	10.3 (1.3)	
	24 hrs	11.6 (2.1)	10.3 (1.7)	11.9 (1.1)	
Biting	2 hrs	3.4 (1.2)	5.6 (1.2)	4.5 (1.0)	
(Sum of R/L)	6 hrs	3.8 (1.3)	7.9 (1.4)	8.0 (1.2)	A < B, C
	Bedtime	2.8 (0.6)	7.4 (1.4)	10.0 (1.2)	A < B, C
	Awakening	6.5 (1.4)	8.2 (1.5)	10.2 (1.1)	A <C
	24 hrs	11.8 (2.0)	9.4 (2.1)	11.7 (1.2)	
Fitting Back	2 hrs	1.2 (0.4)	2.8 (0.6)	1.9 (0.5)	
Teeth Together	6 hrs	2.0 (0.7)	2.9 (0.7)	3.2 (0.6)	
	Bedtime	1.5 (0.4)	3.3 (0.8)	4.4 (0.7)	A < C
	Awakening	3.2 (0.8)	3.6 (0.8)	4.5 (0.6)	
	24 hrs	5.2 (1.0)	4.2 (1.0)	4.8 (0.8)	
Fitting Front	2 hrs	0.4 (0.1)	1.8 (0.6)	0.4 (0.2)	
Teeth Together	6 hrs	0.3 (0.1)	2.4 (0.6)	1.6 (0.5)	A < B
	Bedtime	0.8 (0.3)	2.6 (0.8)	1.7 (0.5)	A < B
	Awakening	2.0 (0.7)	2.6 (0.8)	2.5 (0.5)	
	24 hrs	3.3 (1.1)	2.8 (1.1)	2.7 (0.8)	
Total Pain	2 hrs	8.6 (2.7)	16.1 (3.8)	11.7 (2.5)	
	6 hrs	10.3 (3.3)	20.3 (3.7)	21.3 (3.1)	A < B, C
	Bedtime	8.1 (1.8)	20.7 (4.1)	25.9 (3.1)	A < B, C
	Awakening	19.1 (3.7)	23.6 (4.1)	27.5 (3.2)	
	24 hrs	31.9 (5.7)	26.8 (5.6)	31.1 (3.2)	

[d] Significance based on p-values from mixed models

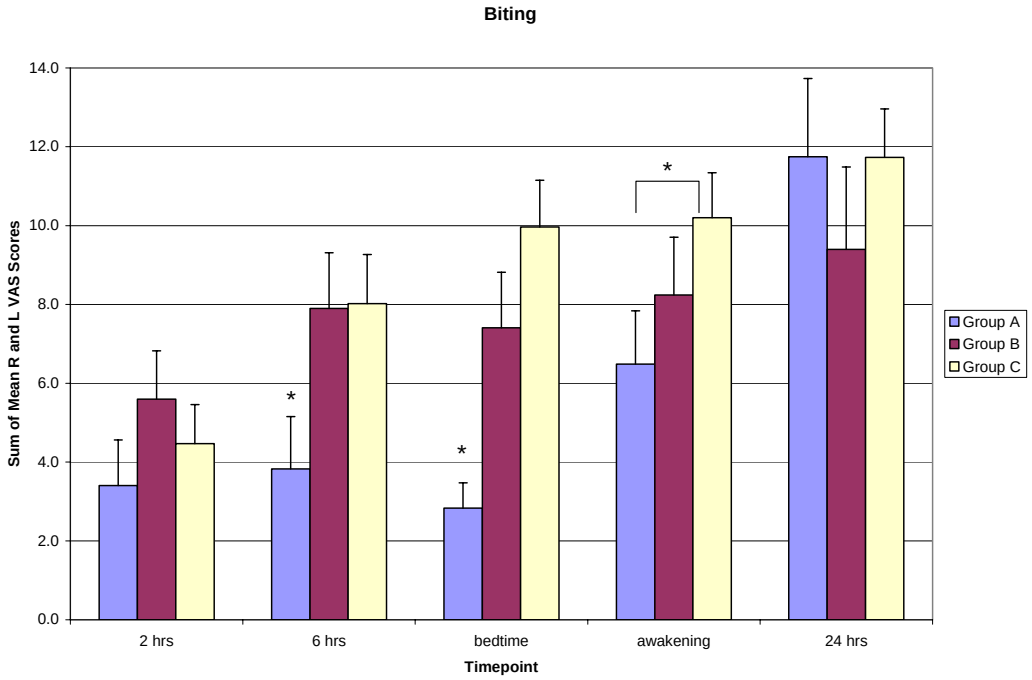

Figure 3-1: Sum of mean VAS scores and standard errors for biting on the right and left sides of the mouth. *p<0.05.

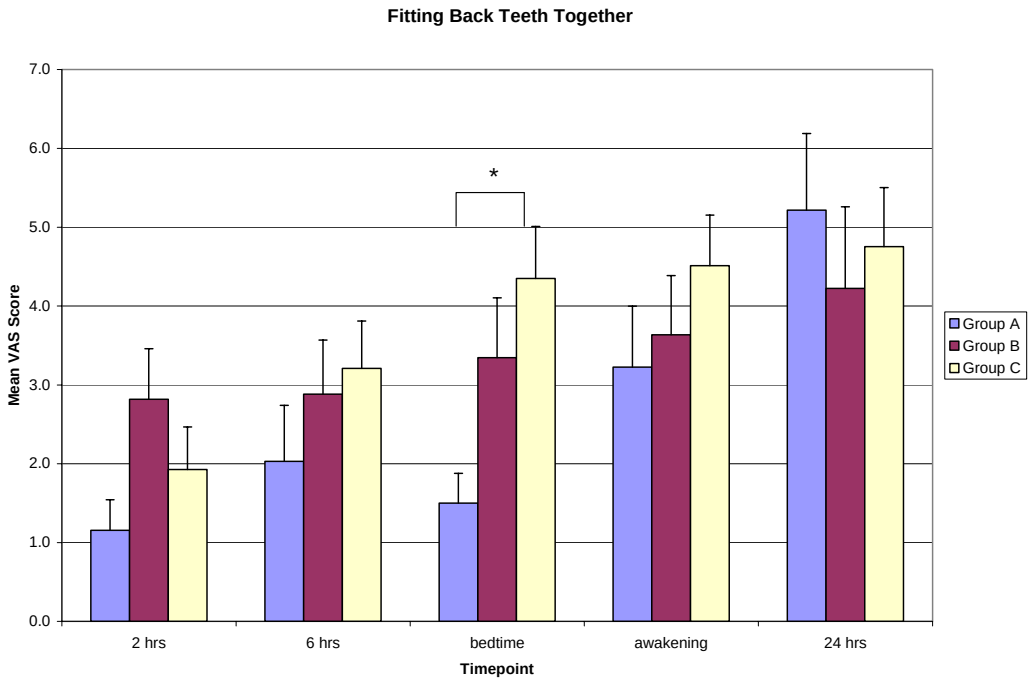

Figure 3-2: Mean VAS scores and standard errors for fitting the back teeth together. *p<0.05.

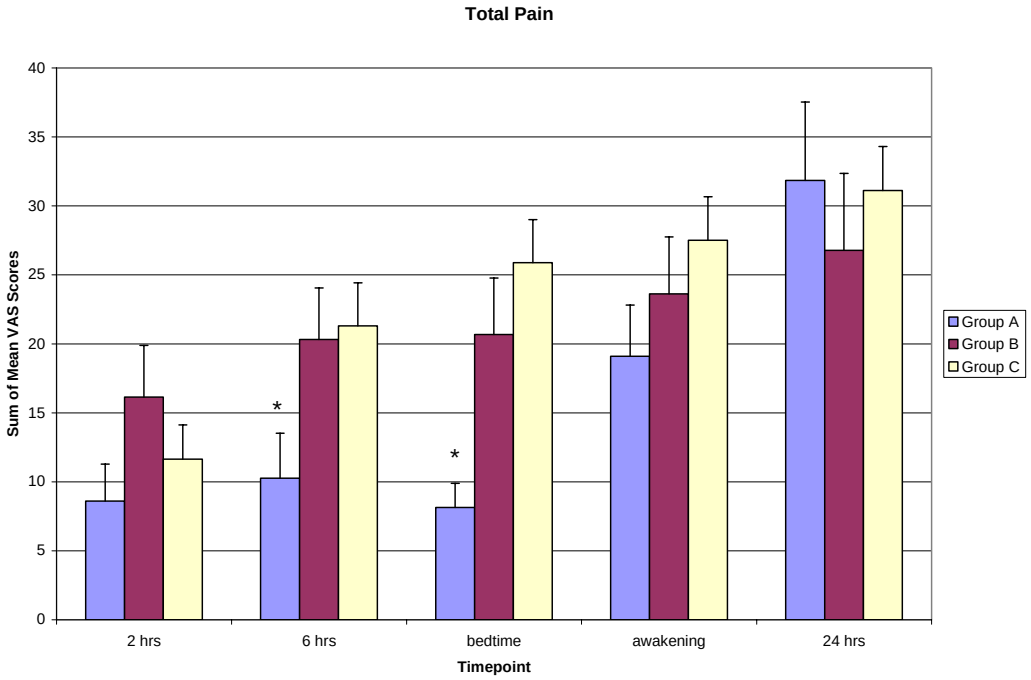

Figure 3-3: Sum of mean VAS scores and standard errors for all categories. *$p<0.05$.

CHAPTER 4
DISCUSSION

The results of this study indicate that less pain is experienced with orthodontic separators if 400 mg ibuprofen is taken collectively at 1 hour before, 3 hours after, and 7 hours after placement. The group that received preemptive and post-treatment ibuprofen (Group A) experienced significantly less pain at 6 hours and at bedtime on the night of separator placement. Group A also reported less pain on the morning after separator placement for biting only. However, for the other categories, the pain experienced by group A increased back up to the same levels as the other two groups by the next morning. There also seemed to be a rebound effect with a trend for group A to report more pain at 24 hours than the other two groups. This rebound effect would indicate that additional doses should be given after the 7-hour dose in order to maintain the benefits of the medication.

Contrary to what would be expected, there was not a significant difference between the pain experienced by the group that took ibuprofen only after separator placement (B) and the placebo group (C) during the first 24 hours. Group B only received post-treatment ibuprofen, and those subjects experienced similar pain levels as the placebo group. This could suggest that once the nociceptive pathway has been initiated, it is difficult to manage the pain with ibuprofen. One might also suppose that the decrease in pain experienced by group A was mainly due to a preemptive anti-inflammatory effect rather than just the analgesic effect of ibuprofen. However, the anti-inflammatory effects of ibuprofen are often not seen for a few days to a week after administration while the

analgesic effects are more immediate. This is evidenced by the higher and more prolonged doses that are recommended for arthritis conditions versus that recommended for pain.[21] Therefore, it is more probable that the benefits of preemptive dosing seen in our study were due to the analgesic properties of ibuprofen rather than the anti-inflammatory effects. Future studies with more prolonged dosing periods are needed to address the anti-inflammatory effects of preemptive ibuprofen. Another possible explanation for the lack of significant differences between groups B and C could be a placebo effect for group C since subjects were told that they had an equal chance of being assigned to any of the three groups. The fact that Group A experienced significantly less pain than Group B but not less than Group C while fitting front teeth together at 6 hours and at bedtime could also be a demonstration of the power of the placebo effect.

It was also found that the amount of pain reported upon placement of separators was a predictor for the amount of pain that would be recorded in the 24 hour pain diary. This could be interpreted two different ways. A method of placement which would cause an increased pain experience during separator placement could produce a more severe inflammatory response that would increase the amount of pain experienced during the first 24 hours. Also, it could be that subjects who report more pain with placement are going to report more pain in the diaries because of their innate pain threshold and tolerance levels.

The results from our study were similar to those of some other studies, but there were also some differences. Ngan et al.[12] found that a single dose of 400 mg ibuprofen taken immediately after separator placement provided more pain relief than placebo at 2 hours, 6 hours, 24 hours, 2 days, and 3 days. The dose in the Ngan et al. study was not

"preemptive", but it was immediately post-treatment. This differs from our study because our Group A received a 1-hour preemptive dose while our Group B received only post-treatment ibuprofen that was not taken until 3 hours and 7 hours after separator placement. In our Group B, the inflammatory cascade was already established by the time any medication was given. This could explain why the Ngan et al. study showed significantly less pain with the early post-treatment ibuprofen group than with the placebo group while ours did not. Law et al.[13] also found significantly less pain at 2 hours for the group that received ibuprofen before separator placement, and similar to our results, they found no significant differences between the placebo group and the group that only received ibuprofen after separator placement. Bernhardt et al.[14] found significantly lower pain levels at 2 hours and at bedtime for the group that only received ibuprofen before separator placement and the group that received both pre-and post-treatment ibuprofen. Polat et al.[15] did not find significant differences between their placebo group and the group that received ibuprofen 1 hour prior to archwire placement, but they did find a trend for less pain at 2 hours and 6 hours. Our study did not find a significant difference between any of the groups for pain at 2 or 24 hours. However, there was a similar trend for our Group A to experience less pain at 2 hours and there were significant differences at 6 hours and at bedtime.

All of these mentioned studies had slightly different results; however that is to be expected with the variations in study design and the multi-dimensional nature of pain. All of the studies used the VAS method for recording pain. Both the Law et al.[13] and Bernhardt et al.[14] studies had small sample sizes due to high incidences of subjects resorting to rescue medication. Our study also had a small sample size, but we had no

requests for rescue medication. This was most likely due to the protocol followed. Subjects and parents were told to call anytime, day or night, if the subject was experiencing enough pain to need medication. At this time, the investigator could instruct the subject or parent on what medication could be taken. The subjects in the Law et al.[13] and Bernhardt et al.[14] studies averaged about 13 years old while those in our study and Polat's[15] study were closer to 16 years old. As previously mentioned, the Polat et al.[15] study involved pain after archwire placement rather than separator placement. Other possible differences could have been in the types of separators that were used or differences in the method of placement, whether over or under the contact of the tooth. Subjects in the Ngan et al.[12] study had separators placed on the mesial and distal of all first molars while subjects in our study had at least one separator placed per quadrant. Although not reported in the studies, there could also have been differences in the times of day that the separators were placed. This could influence results as levels of pain sensitivity may fluctuate throughout the day.

It is not fully understood why our study did not find significant differences at 2 hours while we did at 6 hours, at bedtime, and at time of awakening. Since the peak plasma concentration of ibuprofen is 1-2 hours it would be expected that there would be differences among the groups in pain levels at 2 hours after separator placement. There was a trend for group A to report less pain at 2 hours, and it is possible that a statistically significant difference could be found with a larger sample size. The lack of differences at 24 hours could be explained by the fact that the last dose of ibuprofen was taken 7 hours after separator placement, and the effects had diminished. Another point to consider is that all subjects were given the same dosage of medication without taking weight into

consideration. It is possible that subjects who weighed less could have experienced increased analgesic effects because of the higher concentration of medicine that they received in comparison to heavier subjects.

A commonly accepted principle is that females have a lower pain threshold and less pain tolerance than men. Scheurer et al.[22] found perception of pain to be greater in females than males. McGrath and Craig [23] discovered that pain experiences are reported equally by males and females prior to puberty, but once gender differences emerge, females reported a higher incidence and intensity of pain. Walker and Carmody[24] found that females did not experience a significant analgesic response to ibuprofen while males did. Explanations that have been suggested to account for gender differences include biologic mechanisms such as genetics and hormonal differences and social and psychological factors such as developmental, emotional, and cognitive.[25] Several other investigations into orthodontic pain have discovered no gender differences with regard to prevalence and intensity of pain.[1-3,9,26,27] The results of our study were in agreement with others that have shown no significant gender differences for orthodontic pain. However, our data did show a trend for more pain on separator placement and for a greater increase in pain with the 24 hour masticatory efficiency test for females. It is interesting that studies of other types of pain have found significant gender differences while most of the orthodontic studies have not. This could be because many of the other studies are done on adults while the orthodontic subjects are primarily adolescents. It could also be postulated that females do not perceive as much pain with orthodontics as they would with other pain producing events because of their desire for the esthetic benefits of orthodontic treatment.

Pain is a subjective, multi-dimensional sensation. The experience of pain is extremely variable having contributions from cultural background, previous experience, motivation, gender, personality, and psychological factors.[1-3,22] Firestone et al.[28] concluded that orthodontic patients' expectation of pain is significantly correlated with perceived pain during treatment. Fillingim et al. [29] found that negative affect correlated with lower pain tolerance for both males and females, but it was associated with poorer analgesic response only for males while positive affect was associated with lower pain sensitivity among males only.

Subjects in our study completed two psychological surveys before the first dosing time. The STAI[18] provides a measure of situational anxiety and anxiety as part of personality while the PANAS[19] assesses mood state characterized along the separate dimensions of positive and negative affect. Both of these instruments have demonstrated reliability and validity, and are widely used in clinical and experimental research. Surprisingly, the results from our study did not reveal any contributions from STAI or PANAS for the amounts of pain that were reported with separator placement or in the pain diaries. It was expected that subjects who expected more pain would experience more pain with separator placement. It was also anticipated that subjects with higher anxiety scores, lower positive affect scores, and higher negative affect scores may report higher levels of pain. Perhaps a larger sample size would have produced significant findings for psychological factors.

Studies[30,31] have found prostaglandin application to increase tooth movement in a nearly 2 to 1 ratio. NSAIDs can cause a decrease in tooth movement due to their action in blocking prostaglandin production.[32-34] On the basis of these findings, it has been

suggested that NSAIDs should not be taken during orthodontic treatment to avoid a decrease in tooth movement and an increase in treatment time.[32,33] However, other mediators like leukotrienes, cytokines and growth factors may also contribute to bone resorption.[35] Saito et al.[35] found that indomethacin slowed tooth movement but did not stop it. Tyrovola et al.[34] suggest avoiding only the long-term administration of NSAIDs. Short-term use, as in the present study, will only temporarily reduce the levels of prostaglandins.[12]

While the majority of orthodontic patients would not discontinue treatment because of separator pain, it has been shown that pain does negatively impact compliance.[9,36,37] Because compliance is such a critical factor for successful orthodontic treatment, it is important to be able to control orthodontic pain. Continued research is necessary in order to derive a standard of care for controlling orthodontic pain so that patients will be more comfortable, compliance will be improved, and orthodontic outcomes will be enhanced.

CHAPTER 5
CONCLUSIONS

The following conclusions were drawn from this study.

1) Preemptive administration of ibuprofen can decrease the amount of pain experienced at 6 hours, at bedtime, and on the morning after separator placement.

2) Despite the use of analgesics, there is a decrease in chewing efficiency and an increase in pain on day 2 indicating a need for additional or higher doses or a need for a longer preemptive dosing period.

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BIOGRAPHICAL SKETCH

Valerie Jean Vonnoh Minor was born in Jacksonville, Florida. She graduated from North Carolina State University in 1997 with B.S. degrees in chemical engineering and pulp and paper science and technology. Valerie attended the University of Florida for her dental education and graduated in 2003 with a Doctor of Dental Medicine degree. She then continued her education at the University of Florida, earning a Master of Science with a certificate in the specialization of orthodontics in May 2006.