

ACETAMINOPHEN VERSUS IBUPROFEN FOR THE CONTROL  
OF IMMEDIATE AND DELAYED PAIN FOLLOWING  
ORTHODONTIC SEPARATOR PLACEMENT

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ABSTRACT

The purpose of this investigation was to compare pain control effectiveness of preemptive and postoperative acetaminophen, ibuprofen, and placebo following orthodontic separator placement. Subjects were randomly assigned to 1 of 3 conditions: placebo, 650 mg acetaminophen, or 400 mg ibuprofen. The placebo or analgesic was taken 1 hour prior to separator placement and 6 hours thereafter. Pain on chewing, teeth touching and biting was recorded on Visual Analogue Scales at 6 time intervals over 24 hours. Pain increased immediately after separator placement, decreased at 2 hours, then increased with variation into the next day. While preemptive analgesic decreased initial pain levels, no similar benefit was found from the postoperative dose. Differences between the two analgesics were not statistically significant, and no more effective than the placebo. Preemptive acetaminophen and ibuprofen are equally effective in controlling early pain following separator placement.

The undersigned, appointed by the Dean of the School of Dentistry, have examined a thesis titled “Acetaminophen versus Ibuprofen for the Control of Immediate and Delayed Pain Following Orthodontic Separator Placement,” presented by Shelliann A. Kawamoto, candidate for the Master of Science degree, and hereby certify that in their opinion it is worthy of acceptance.

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## CHAPTER 1

### INTRODUCTION

Pain control during orthodontics is a common concern for the orthodontist as well as for the patients seeking orthodontic treatment. Unfortunately, orthodontists may be unaware of the extent of their patients' pain experiences since subjects may begin feeling significant levels of pain hours after the office visit (Ngan et al. 1994; Steen Law et al. 2000; Bernhardt et al. 2001; Erdinc and Dincer 2004; Bird et al. 2007). Several studies have concluded that the vast majority of patients will experience pain at some point during orthodontic care (Kvam et al. 1987; Lew 1993; Scheurer et al. 1996; Bergius et al. 2002; Bergius et al. 2008). Although the degree of pain experienced will be perceived differently between individuals, some patients consider orthodontic pain to be greater in incidence and severity than pain experienced from tooth extractions (Jones and Chan 1992; Bernhardt et al. 2001; Bird et al. 2007). According to a survey of patients' attitudes towards orthodontic treatment, patients felt that discomfort was the most discouraging factor during treatment, as well as the most likely reason for discontinuing care (Oliver and Knapman 1985; Bernhardt et al. 2001; Bird et al. 2007).

#### Dental and Orthodontic Pain

Pain, according to the International Association for the Study of Pain (IASP), is described as a sensory and emotional experience that is considered unpleasant and is associated with some type of actual or potential tissue damage (Merskey and Bogduk 1994).

Pain impulses from the oral cavity travel directly into the brainstem via the trigeminal nerve (CN V), which is the largest nerve that contributes to the orofacial structures. Impulses

from the brainstem pons then travel to the trigeminal spinal nucleus and onward to the anterolateral spinothalamic tract in higher brain centers. Impulses ascend reaching the reticular formation where they are monitored and filtered. Information will then continue to the thalamus and cortex where they will be perceived as pain (Okeson 1996).

Orthodontics is the branch of dentistry that specializes in the diagnosis, prevention, and correction of dental malocclusions and facial irregularities. Orthodontic treatment involves application of forces with functional appliances or other corrective appliances such as braces. Occasionally prior to application of braces, separators approximately 1.4 mm wide are placed between posterior teeth to push teeth apart, creating space for the future placement of orthodontic metal bands. Discomfort from separator placement has been described as "annoying," "sore," and "tight" (Bird et al. 2007).

Although it is still unclear why pain arises during orthodontic tooth movement, it is thought that tooth movement produces two different pain responses, immediate and delayed. Application of orthodontic forces result in tooth movement and compression of the periodontal ligament (PDL), as well as an instantaneous immediate pain response (Burstone 1962). Compression of the PDL produces areas of ischemia, inflammation, and edema in the PDL space with an increase in pressure and a decrease in blood flow (Furstman and Bernick 1972). Mechanical deformation of pressure receptors mainly located in the apical two-thirds of the root PDL space results in the synthesis of prostaglandins (PGs), mediators of inflammation (Saito et al. 1991; Proffit and Fields 2000). Dissemination of painful stimuli is enhanced by PGs, resulting in early pain (Ferreira et al. 1978). Therefore, pain experienced

during early tooth movement is the result of PDL compression and the subsequent PG enhanced inflammatory response.

The delayed pain response usually occurs a few hours after application of orthodontic forces due to PG induced hyperalgesia of the PDL, which is a reduction in pain threshold resulting in increased sensitivity to noxious stimuli (such as histamine, bradykinin, serotonin, acetylcholine, and substance P) that are released after PDL compression and activation of the inflammatory reaction. These stimuli are released at the site of tissue damage and result in an increase in the transmission of pain signals (Burstone 1962; Higgs and Moncada 1983).

The separation of the molars using elastic separators is usually necessary to create space for placement of metal bands. This procedure, along with the arch wire adjustments to follow, can produce some level of discomfort (Ngan et al. 1989; Ngan et al. 1994; Bergius et al. 2000; Steen Law et al. 2000; Bernhardt et al. 2001; Bondemark et al. 2004; Erdinc and Dincer 2004; Polat and Karaman 2005; Polat et al. 2005; Giannopoulou et al. 2006; Bird et al. 2007; Bradley et al. 2007; Minor et al. 2009; Salmassian et al. 2009). Ngan, Kess, and Wilson (1989) investigated the effect of separator placement and arch wire placement on subject discomfort over time. Ninety-nine subjects, age range from 10.5 to 38 years, were recruited to log their discomfort levels at six time intervals: 4 hours, 24 hours and 7 days after separator placement, and 4 hours, 24 hours and 7 days after initial arch wire insertion. Of the 99 subjects, 29 subjects who were not scheduled for orthodontic treatment served as the control group and the remaining 70 subjects comprised the experimental group. Five experimental subjects were dropped due to inadequate understanding of the scoring system. Sixty-five experimental subjects completed the 7-day separator study and 57 of those

subjects continued on to complete the 7-day arch wire study. In both separator and arch wire assessments, discomfort levels at the 4 and 24 hours intervals were found to be significantly different from the control group while discomfort levels at the 7 day interval did not differ from the control group. The authors determined that discomfort levels increased 4 hours after treatment, peaked at 24 hours and then decreased to almost baseline levels by day 7. The same authors, Wilson, Ngan and Kess (1989) then sought out to determine the time window of discomfort in the young patients 10-16 years of age that were included in their previous study. Excluding the data from those in the initial data set over the age of 16, fifty-nine adolescents were included with 45 subjects in the experimental group and 14 in the control group. The results concurred with the larger sample that discomfort levels increased 4 hours after treatment, continued for a minimum of 24 hours and then dissipated by one week. Orthodontists may not be aware of their patients' delayed pain which can intensify up to 24 hours post-treatment, long after subjects' leave the office. Therefore, methods to control both immediate and delayed pain needs to be investigated and implemented.

#### Control of Orthodontic Pain

During orthodontic treatment, patients will experience variable levels of discomfort with tooth movement (Ngan et al. 1994; Bergius et al. 2002; Bird et al. 2007). Despite the fact that pain control is of significant interest to both orthodontists and their patients, limited research exists regarding the control of orthodontic pain and currently no standard of care exists to eliminate the discomfort (Ngan et al. 1994; Steen Law et al. 2000; Bernhardt et al. 2001; Bergius et al. 2002; Bird et al. 2007). In current dental research, there has been a shift towards investigating methods for prevention of pain rather than the control of existing pain

(Steen Law et al. 2000; Bernhardt et al. 2001; Bird et al. 2007; Bradley et al. 2007; Minor et al. 2009). Oral analgesics such as ibuprofen and acetaminophen continue to be the most common method utilized to alleviate dental pain, as well as to prevent the pain response preemptively (Bergius et al. 2000; Bradley et al. 2007).

### Nonsteroidal Anti-inflammatory Drugs (Ibuprofen)

Prevention of pain involves the administration of a preemptive (preoperative) analgesic to block immediate peripheral sensitization and prevent the subsequent central sensitization. Therefore the goal of oral analgesics is to block prostaglandin synthesis and abolish the nociceptive afferent nerve impulses before they reach the central nervous system preventing central sensitization and resultant pain (Woolf 1991; Golinski and Fill 1995). One family of oral analgesics, the nonsteroidal anti-inflammatory drugs (NSAIDs), are peripherally active compounds characterized by varying degrees of anti-inflammatory, analgesic, and antipyretic activity. Ibuprofen, one type of NSAID, suppresses PG biosynthesis at the site of inflammation or injury by inhibiting cyclooxygenase (COX), an enzyme necessary for the formation of PG. This results in suppression of the inflammatory process and associated pain. The recommended adult analgesic dose is 200-400 mg every 4-6 hours while pain persists, with a maximum of 1.2 grams in a 24-hour period. For children aged 6 months to 12 years, the recommended analgesic dose is 4-10 mg/kg every 6-8 hours, with a maximum of 40 mg/kg/day. Onset of action occurs within 30-60 minutes and reaches maximal concentration in 1-2 hours. Duration of action is 4-6 hours with a half-life of 2 hours (Burton et al. 2006; Wynn et al. 2006). If given preoperatively, the body has adequate time to absorb and distribute the medication before tissue injury and production of PGs

occurs, therefore minimizing the production of PGs, inflammatory response and pain (Kehoe et al. 1996; Steen Law et al. 2000; Bernhardt et al. 2001; Polat and Karaman 2005; Polat et al. 2005; Minor et al. 2009).

There have been several studies that have investigated the effectiveness of ibuprofen on pain control. Ngan and others (1994) conducted another study on pain levels following separator placement, however this time incorporating the use of orally administered analgesics. The purpose of the randomized, double blind, single analgesic dose study was to compare analgesic effectiveness of ibuprofen (400 mg), aspirin (650 mg), and a placebo (beta-lactose) for control of postoperative pain following placement of separators. Seventy seven subjects were instructed to take their assigned medication immediately after separator placement and to log their discomfort levels using discomfort index cards at time 0 (just prior to treatment), 2, 6, and 24 hours, and 2, 3, and 7 days later. The discomfort index card consisted of four 10 cm VAS lines where the subject marked discomfort levels during chewing, biting, fitting their back teeth together, and fitting their front teeth together. Descriptive terms of discomfort levels were present at both ends of each VAS line along with corresponding "happy" and "sad" faces. For all groups, pain persisted through the 7-day evaluation period, gradually increasing to a peak at the 24 hour time period then gradually decreasing. The placebo group had significantly more discomfort than the ibuprofen group at all time periods except at baseline and at 7 days. It was concluded that the placebo group experienced significantly more pain than the aspirin group, whereas the least discomfort was noted with the ibuprofen group. The authors concluded that a single dose of ibuprofen taken immediately after separator placement significantly lowered pain levels post-treatment



compared to a placebo. In this study, ibuprofen was taken after separator placement. Since ibuprofen has an onset of 30-60 minutes and reaches maximal concentration 1-2 hours after administration, its peak effect will occur after the onset of inflammation and production of prostaglandins (immediate pain response). Therefore, the results of this study reflect the superior effectiveness of ibuprofen on the delayed pain response that occurs a few hours after treatment.

Steen Law and others (2000) conducted a prospective study to investigate the effect of ibuprofen on the immediate and delayed pain response by incorporating a single ibuprofen dosage taken either before or after separator placement. Sixty three subjects were randomized into one of three groups: (1) ibuprofen (400 mg) taken orally 1 hour prior to separator placement and a lactose placebo taken orally immediately following treatment, (2) a lactose placebo taken orally 1 hour prior to separator placement and ibuprofen (400 mg) taken orally immediately following treatment, or (3) a lactose placebo taken orally 1 hour prior to separator placement and again immediately after treatment. Subjects were asked to complete visual analogue scale (VAS) questionnaires at 2, 6, and 24 hours, and 2, 3 and 7 days after separator placement. Two hours after separator placement, subjects who had taken ibuprofen prior to treatment reported significantly less pain ( $9.5 \pm 11.6$ ) compared to subjects who had taken pretreatment placebo and post-treatment ibuprofen ( $20.9 \pm 21.7$ ) or placebo both before and after treatment ( $25.2 \pm 27.8$ ). No other significant differences were found at any other time interval. All three groups reported an increase in pain from the 2-hour assessment to a maximum peak at 24 hours. Preemptive ibuprofen, taken 1 hour prior to separator placement allowed time for adequate levels of the drug to reach the peripheral

tissues to block the immediate pain response. This resulted in decreased pain levels up to the 2-hour time period. Subjects who received pre-treatment placebo and ibuprofen immediately after treatment did not experience the expected decrease in pain. In this group, the immediate pain response that occurred during separator placement had already initiated the cascade of events causing peripheral and central sensitization prior to the post-treatment ibuprofen dose. Since ibuprofen acts primarily in the peripheral tissues, post-treatment ibuprofen was unable to reverse the present pain experience. It was concluded that a 1-hour preemptive dose of ibuprofen might be effective in reducing orthodontic pain 2 hours after separator placement.

Average peak pain from orthodontic separators was found to occur most frequently in a period upon rising the day after the orthodontic visit (17 hours) through 24 hours (Ngan et al. 1994; Steen Law et al. 2000; Bernhardt et al. 2001; Bergius et al. 2002; Bird et al. 2007; Bradley et al. 2007). Since the recommended adult dose of ibuprofen is 200 to 400 mg every 4 to 6 hours while pain persists, it was questionable whether a single preemptive dose of ibuprofen would continue pain control up to 24 hours. Therefore, the effect of ibuprofen administered both pretreatment and post-treatment on the delayed pain response warranted investigation. Bernhardt and others (2001) compared the effectiveness of preemptive ibuprofen, postoperative ibuprofen, or a multiple dose combination therapy on forty-one orthodontic subjects who were appointed for separator placement. The subjects were randomly assigned to receive either 400 mg ibuprofen 1 hour pre-treatment and 6 hours after the initial dose, 400 mg ibuprofen 1 hour pre-treatment and a lactose capsule 6 hours after the initial dose, or a lactose capsule 1 hour pre-treatment and 400 mg ibuprofen 6 hours after the

initial placebo. No true control group with both pre-treatment and post-treatment placebo was included for comparison in this study. The authors concluded that for all subjects after separator placement, peak pain occurred most frequently upon rising the day after separator placement (17 hours), second most frequent at 24 hours with a gradual decrease in pain levels through the 7th day. Two hours post-treatment, subjects who received ibuprofen prior to separator placement reported significantly less pain ( $4.3 \pm 5.1$  and  $9.0 \pm 14.8$ ) than those who were given a pre-treatment placebo ( $30.1 \pm 33.2$ ). At bedtime, subjects who received only pretreatment ibuprofen reported significantly less pain ( $20.1 \pm 28.3$ ) than those who were given only post-treatment ibuprofen ( $46.2 \pm 38.3$ ). The multiple dose regimen of ibuprofen, administered before and after separator placement, enabled a limited amount of analgesic ability to extend into day two, however, this was not statistically significant in comparison to subjects who received preemptive ibuprofen alone. Therefore the authors could only conclude that 400 mg ibuprofen taken 1 hour prior to separator placement is effective in reducing discomfort through bedtime (10 hours) when compared to post-treatment ibuprofen alone. Possible lack of statistical significance for the extension of pain control into day 2 may be attributed to several limitations of this study. One hundred fourteen subjects were recruited for the study, however only 63 questionnaires were returned. Out of those 63, 22 subjects had taken additional analgesics and were subsequently excluded from the study resulting in a small sample size of 41. Other limitations included large standard deviations resulting from a wide range of individual variation, and uneven gender distribution regardless of the randomization process. These limitations affected the power of the study and results in questionable statistical conclusion validity.

Other studies on separator placement have yielded different results. Minor and others (2009) conducted a prospective study comparing post-separator pain levels in subjects receiving preemptive ibuprofen, preemptive placebo, or multiple dose postoperative ibuprofen. Forty-one subjects were randomly assigned into 1 of 3 groups: 400 mg of ibuprofen 1 hour prior to separator placement, then again at 3 and 7 hours after treatment; placebo 1 hour pre-treatment then 400 mg ibuprofen at 3 and 7 hours post-treatment; and, placebo 1 hour pre-treatment and at 3 and 7 hours post-treatment. As expected, the ibuprofen group experienced less pain than the other two groups, with statistically significant difference found at 6 hours and at bedtime. There was no significant difference in pain experience between two preemptive placebo groups (with and without ibuprofen post treatment), suggesting that the significant reduction in delayed pain experienced with ibuprofen might be attributed to a preemptive anti-inflammatory effect. The authors did not find significant differences in pain control at 2 hours and they postulate that significance would have been achieved with a larger sample size. In agreement with past studies, pain was the greatest at 24 hours despite their multiple dose strategy. The lack of difference at 24 hours may be due to decreased effects of the last dose given 7 hours after separator placement. Therefore, more dosages may be necessary to extend pain control into day 2. It was concluded that delayed pain at 6 hours and at bedtime may be reduced with a multiple dose strategy that includes a preemptive dose.

While ibuprofen has demonstrated analgesic benefits, several animal studies have shown that this agent slows orthodontic tooth movement (Kehoe et al. 1996; Arias and Marquez-Orozco 2006; Bartzela et al. 2009). Orthodontic tooth movement involves bone

resorption and apposition. PGs have been postulated to mediate bone resorption by stimulating lymphocytes and macrophages, ultimately leading to an increase in osteoclast numbers and elevated levels of lysosomal enzymes and collagenase. The importance of PG role in the mechanics of tooth movement have been demonstrated by studies of direct application of PGE1 or PGE2 and the resultant increase tooth movement in both rats and humans (Yamasaki et al. 1982; Sekhavat et al. 2002; Gurton et al. 2004; Kale et al. 2004; Salmassian et al. 2009). Anti-inflammatory agents such as ibuprofen block the peripheral synthesis of PGs, resulting in a consistent inhibition of localized osteoclastic bone resorption and therefore, a reduced rate of tooth movement (Kehoe et al. 1996; Walker and Buring 2001; Arias and Marquez-Orozco 2006; Minor et al. 2009).

Kehoe and others (1996) investigated the effect of various analgesics on orthodontic tooth separation in forty male guinea pigs. The guinea pigs were randomly assigned to one of four groups: (1) control (0.4% carboxymethylcellulose 1.66 ml/kg q 12 h), (2) misoprostol (100 µg/kg q 12 h), (3) acetaminophen (200 mg/kg q 12 h), and (4) ibuprofen (30 mg/kg q 12 h). Drugs were administered 1 hour prior to bonding of a titanium molybdenum alloy torsion spring interproximally between the maxillary central incisors. Each TMA spring was measured to exert a force of  $25 \pm 1$  gm. Separation measurements were recorded at 2, 4, 6, 8, 10, and 11 days using a digital measuring caliper. At day 11, the misoprostol group exhibited the greatest amount of tooth separation ( $4.49 \pm 0.49$  mm), the ibuprofen group resulted in the lowest amount of tooth separation ( $2.56 \pm 0.11$  mm) while the control and acetaminophen group exhibited similar amounts,  $3.31 \pm 0.07$  mm and  $3.31 \pm 0.08$  mm, respectively. Compared to the control group, ibuprofen reduced tooth movement by

approximately 0.75 mm during an 11 day time period. Theoretically, if orthodontic subjects were to continue ibuprofen therapy throughout the duration of treatment, the loss of 0.75 mm every 11 days during a 24 to 36 month treatment period could significantly increase treatment time. Since the dosages administered in this study were higher than the amounts normally given for human pain control, it is not certain that similar reductions in tooth movement would occur for humans, however the possibility of a decrease in tooth movement and increase in treatment time is of concern. Therefore, it would be in the best interest of the orthodontist and subject to utilize an effective analgesic that lacks the ability to slow orthodontic tooth movement (Salmassian et al. 2009).

#### Acetaminophen

Acetaminophen is considered to be a very weak prostaglandin inhibitor with levels of analgesia comparable to the NSAIDs but without anti-inflammatory properties since it does not concentrate in the areas of inflammation. Acetaminophen functions to inhibit central nervous system PG synthesis and block nociceptive impulses peripherally (Roche et al. 1997; Burton et al. 2006; Wynn et al. 2006). While NSAIDs block COX-1 and/or COX-2 isoforms, acetaminophen blocks the isoform found only in the brain and spinal cord, COX-3, therefore minimizing the effects on PG synthesis and tooth movement (Bartzela et al. 2009). The recommended adult analgesic dose is 325 to 650 mg every 4 to 6 hours with a maximum of 4 grams in a 24-hour period. For children less than 12 years of age, the recommended analgesic dose is 10-15 mg/kg every 4-6 hours, with a maximum of 2.6 g/day. Onset of action occurs in less than 1 hour and reaches maximal concentration in 0.25 to 2 hours.

Duration of action is 4-6 hours with a half-life of 1.5 to 3 hours (Roche et al. 1997; Burton et al. 2006; Wynn et al. 2006).

Although the exact mechanism of action is not completely understood, acetaminophen is thought to inhibit PG synthesis within the central nervous system, not in the periphery (Wynn et al. 2006). Since acetaminophen does not function as an anti-inflammatory agent in peripheral tissues, it should not have an effect on peripheral PG synthesis and, therefore, should not disrupt orthodontic tooth movement like NSAIDs. Several animal studies have investigated the potential for acetaminophen to provide analgesia while maintaining the rate of orthodontic tooth movement (Kehoe et al. 1996; Roche et al. 1997; Arias and Marquez-Orozco 2006). Ibuprofen and aspirin continually demonstrated less tooth movement than acetaminophen (Kehoe et al. 1996; Arias and Marquez-Orozco 2006; Bartzela et al. 2009). Arias and Marquez-Orozco (2006) studied the effect of aspirin, acetaminophen and ibuprofen on orthodontic tooth movement in 36 Wistar rats. They also investigated the histological difference in bone resorption found in pressure areas. Aspirin and ibuprofen resulted in significantly lower numbers of resorption lacunae and osteoclasts in pressure areas and significantly slower dental movement than the control or acetaminophen group. Acetaminophen did not significantly reduce the amount of resorption lacunae or osteoclasts, and exhibited tooth movement very similar to that of the control group.

If acetaminophen, unlike ibuprofen, has a primary mode of action concentrated on central nervous system PG synthesis without effects on orthodontic tooth movement, it would seem appropriate that acetaminophen would be the ideal drug of choice for orthodontic patients if pain control levels are comparable. Bird, Williams and Kula (2007)

conducted an investigation to evaluate the analgesic effectiveness of preoperative acetaminophen and ibuprofen following orthodontic separator placement. Thirty-three orthodontic subjects were randomly assigned to receive either a single dose of acetaminophen (650 mg) or ibuprofen (400 mg) to be taken 1 hour prior to separator placement. Subjects were asked to record their discomfort level on visual analogue scales (VAS) and McGill pain questionnaires (MPQ) at five different time intervals: immediately prior to separator placement, immediately following separator placement, 2 to 3 hours after placement, at bedtime, and upon rising the next day. Subjects were also asked to choose words from a list that describe their pain at the various time intervals. “Annoying” was the most commonly selected word immediately after separator placement and 2 to 3 hours later, while “sore” became the most common word at bedtime and upon waking the next morning. There was no significant difference in pain levels between acetaminophen and ibuprofen given 1 hour prior to separator placement. Subjects reported that pain increased immediately following separator placement, then decreased at 2 to 3 hours post-treatment, then gradually increased to a peak the following morning. This trend demonstrates the preoperative analgesic effect on the immediate pain response and shows that there was no effect on the delayed pain response that usually begins 2 hours post-treatment. No statistically significant difference in pain at any time interval was noted for either experimental medication. Therefore acetaminophen may be a reasonable alternative for prevention of mild orthodontic pain, however multiple dosages may be needed to continue pain control throughout the duration of discomfort.



Bradley and colleagues (2007) utilized a different methodological approach to explore the comparative effectiveness of ibuprofen and paracetamol (acetaminophen). Their design and statistical analysis was based on equivalence (non-inferiority) of the 2 drugs as preemptive pain control for separator placement. Using the VAS to measure pain control, the researchers defined the non-inferiority margin as being within  $\pm 10$  mms on the pain scale relative to the other medication. One hundred fifty-nine subjects aged 12 to 16 years old were randomly assigned to 1 of 2 experimental groups. Group A received 1 g of paracetamol to take 1 hour prior to separator placement and 6 hours later, while Group B received 400 mg of ibuprofen to take 1 hour pretreatment and 6 hours later. All subjects recorded their discomfort on VAS at 2 hours after separator placement, 6 hours after placement, at bedtime, on arising the next morning, and on arising 2, 3 and 7 days after the appointment. No baseline discomfort levels were recorded. Of the 176 patients recruited, 28 were excluded for not fulfilling the inclusion criteria or for failing to return the questionnaire. Their results showed that a composite pain score (averaged across the 2, 6 and bedtime measures) for acetaminophen was not equivalent to ibuprofen (e.g., pain scores were higher for acetaminophen within the 95% CI). However, ibuprofen was statistically better than acetaminophen at 2 hours when results were compared at each observation. It is important to note that the study did not employ a true control group against which pain scores could be compared. Furthermore, 11% of patients needed additional medication suggesting that more doses or higher dosages may be needed to sufficiently prolong control of orthodontic separator pain.

Lack of negative effect on tooth movement enables acetaminophen to be considered a viable alternative for control of orthodontic pain. For those reasons, some authors have suggested that acetaminophen should be considered to be the analgesic of choice during orthodontic treatment (Kehoe et al. 1996; Roche et al. 1997; Walker and Buring 2001; Arias and Marquez-Orozco 2006; Bartzela et al. 2009). However, since acetaminophen is free of anti-inflammatory properties and pain from orthodontic forces appears to be secondary to the inflammatory process, its efficiency in pain alleviation compared to NSAIDs remains questionable. Only two published studies have compared the effectiveness of acetaminophen to ibuprofen for the control of orthodontic separator pain on human subjects and their conclusions were in opposition (Bird et al. 2007; Bradley et al. 2007). Bird and others (2007) were the first to compare effectiveness of single preemptive dosages of acetaminophen and ibuprofen for the control of orthodontic separator pain. No statistical difference in pain was found for either medication at any time interval. Bradley and others (2007) incorporated multiple dosage periods to study pain control over time since average peak pain from orthodontic separators was found to occur most frequently upon rising the day after the orthodontic visit (17 hours) and next at 24 hours. Subjects were assigned to receive either preemptive and postoperative paracetamol (acetaminophen) or preemptive and postoperative ibuprofen. Ibuprofen was found to be significantly better than paracetamol from 2 hours to bedtime. Both studies were conducted without a placebo group for control.

To date, there is no established protocol for control of orthodontic discomfort. If there is a chance that ibuprofen slows the rate of tooth movement, and no advantage of ibuprofen over acetaminophen in pain control effectiveness, it would be prudent for

orthodontists to recommend acetaminophen as the drug of choice for the control of orthodontic pain. Although more studies evaluating pain control using variable types of analgesics and time dose intervals are surfacing, results of effectiveness have been inconsistent. Therefore, this study will compare pain control effectiveness of preemptive and postoperative acetaminophen and ibuprofen compared to placebo therapy following separator placement.

#### Problem Statement

The purpose of this randomized, double blind, prospective clinical study is to compare the pain control effectiveness of preemptive and postoperative acetaminophen and ibuprofen to placebo therapy following separator placement.

#### Hypothesis

There will be a significant difference in post-separator placement pain measured during three conditions using visual analogue scales over six time periods and this effect will differ between acetaminophen, ibuprofen and placebo.

## CHAPTER 2

### MATERIALS AND METHODS

#### Experimental Research Design

The design of this study is a randomized, double blind, 3 parallel arms, longitudinal, multiple dose, placebo controlled prospective clinical trial with measurement of pain using visual analogue scales (VAS) during three conditions: teeth not touching, chewing, and biting back teeth together.

Visual analogue scales are widely utilized in dental pain studies for its reliability and simple concept (Ngan et al. 1989). In a 1989 orthodontic pain study by Ngan and others, patients were asked to complete a 14 VAS discomfort index card during conditions of chewing, biting, fitting back teeth together, fitting front teeth together, speech, popping and clicking of jaw joint, appearance of teeth, facial profile, general appearance, general health, feelings about self, socializing, performance in work or school, and being out in public. More recent studies have lessened the number of VAS, limiting their data collection to those conditions pertaining to dental pain and function (Ngan et al. 1994; Steen Law et al. 2000; Bernhardt et al. 2001; Bird et al. 2007; Bradley et al. 2007). In our study, pain was evaluated during three conditions that were previously evaluated in a similar study by Bird and others (2007): when teeth were not touching, when chewing, and when biting back teeth together.

Visual analogue scale evaluations of pain were obtained at the following time intervals: immediately before separator placement, immediately after separator placement, 2 hours post-placement, 6 hours post-placement, bedtime and 24 hours post-placement (Fig.1) (Moher et al. 2010; Schulz et al. 2010). The rationale for this decision was based on

analgesic onset of action and drug half-life times. Acetaminophen onset of action occurs in less than 1 hour and ibuprofen onset of action occurs within 30-60 minutes. Analgesics dosage 1 hour prior to separator placement should allow sufficient time for analgesic concentrations to prevent peripheral and central PG biosynthesis and control the immediate pain response that occurs immediately following separator placement. Pain control will lessen gradually based on analgesic half-lives, 2 hours for ibuprofen and 1.5-3 hours for acetaminophen. A 2-hour half-life will allow approximately 12.5% of the original analgesic concentration to remain 5 hours post-placement (6 hours after the initial dose). At that time, prior to complete elimination of the first dose, a second dose of analgesic will be administered to allow extended prevention of PG biosynthesis and pain control. The second dose will take action within 1 hour; therefore a 6-hour post-placement evaluation is scheduled to evaluate that effect. Evaluations will also be performed at bedtime and at 24 hours to determine if this dosage strategy will extend pain control over time.

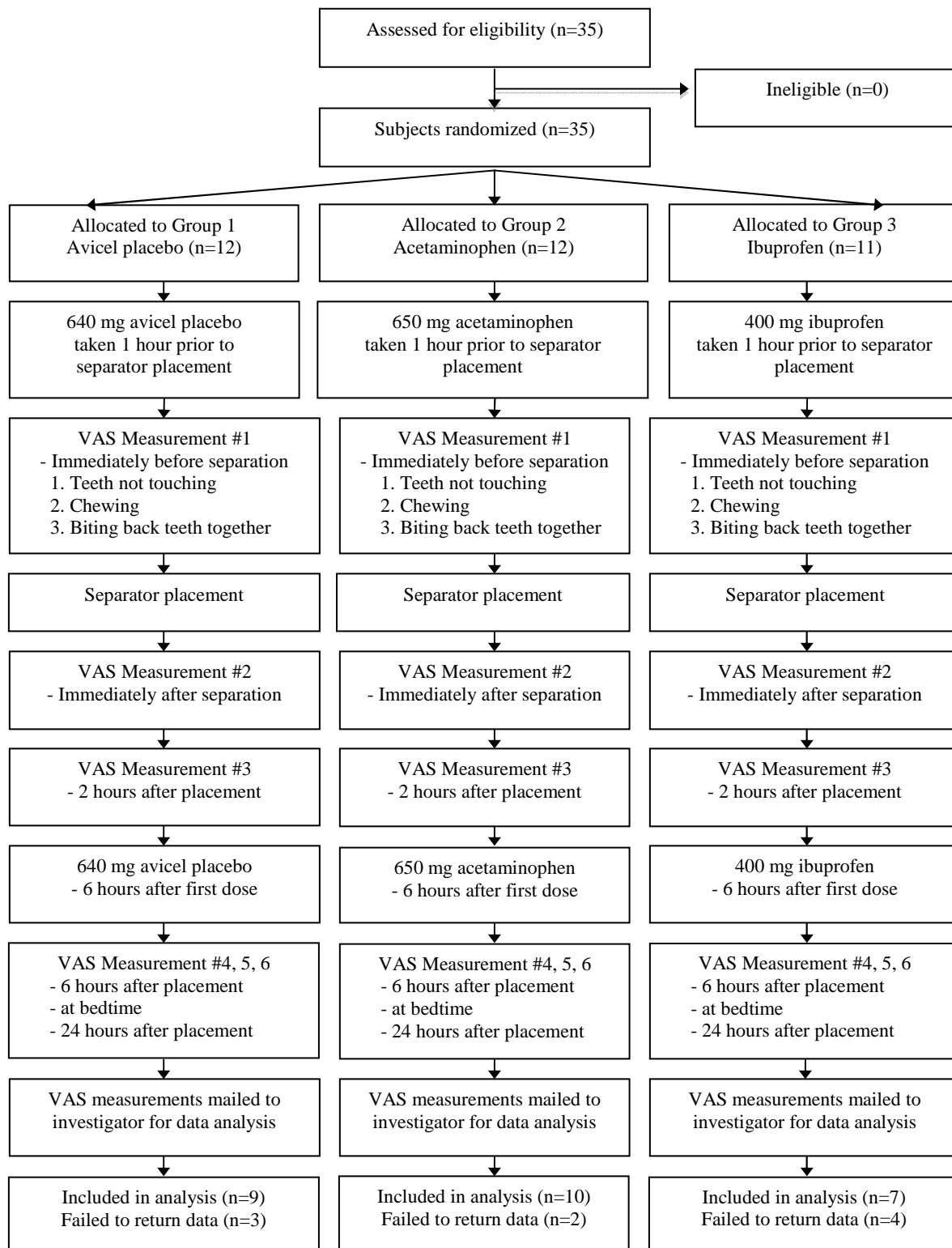


Fig. 1. Flow diagram of placebo versus acetaminophen and ibuprofen for control of orthodontic separator pain.

### Experimental Procedures

Following approval by the Children's Mercy Hospital Pediatric Institutional Review Board, two orthodontists who agreed to have their patients participate in the study signed a letter of agreement to participate. At the consultation appointment, parents and subjects were given a verbal and written explanation of the study, and parental informed consent and child's assent were obtained prior to enrollment in the study. Subjects who met the inclusion criteria were enrolled and given a packet containing an instruction sheet and a sealed numbered envelope with the first dose (2 tablets) of placebo, acetaminophen, or ibuprofen, to be taken 1 hour prior to the scheduled separator placement appointment.

A total of 35 subjects from two private orthodontic offices in Lee's Summit, Missouri, met the inclusion criteria and agreed to participate in this 24-hour study. The selection criteria were as follows: (1) starting orthodontic treatment that required banding of posterior teeth and placement of two or more separators, (2) able to swallow analgesic pills, (3) English speaking, (4) 9 to 17 years of age, and (5) minimum weight requirement of 88 pounds based on mg/kg pediatric dosage recommendations. Subjects were excluded from the study if they had current orthodontic or space maintenance appliances, if there was a contraindication to the use of acetaminophen or ibuprofen, if they were currently taking antibiotics or analgesics, had any cognitive impairment, or any systemic disease that in the assessment of the investigator might impact pain perception.

Subjects were randomly assigned to 1 of 3 experimental groups: 640 mg avicel placebo (two 320 mg capsules), 650 mg acetaminophen (two 325 mg capsules), or 400 mg

ibuprofen (two 200 mg capsules). All treatment groups received an initial dose to be taken 1 hour prior to separator placement and a second dose to be taken 6 hours after the initial dose.

The ibuprofen, acetaminophen, and placebo tablets were compounded by a licensed pharmacist (O'Brien Pharmacy, Kansas City, MO) according to specifications and were all provided in identical white opaque capsules. Medications and placebo tablets were packed and distributed in sealed, coded envelopes. Computer generated random patient coding and group allocation was utilized so that subjects, parents, and the investigator would be blinded as to the group assignments. The random allocation assignments were concealed and inaccessible to the investigator.

Subjects were instructed to take one dose of their assigned drug (2 tablets) 1 hour prior to the scheduled separator appointment and record the time it was taken. At the orthodontic office, just prior to separator placement, the subject was given a VAS pain assessment form comprised of three horizontal lines, each 10 cm (100 mm) in length. Each line was marked with descriptors at each end stating "no pain" or "worst pain imaginable" with corresponding happy or unhappy faces (Appendix 1). Subjects were instructed to make one small vertical mark on each line to indicate how their teeth felt when their teeth were not touching, when chewing, and when biting their back teeth together. Orthodontic separators<sup>1</sup> were then placed in the necessary contacts and the attending clinician recorded the number of separators in order to determine if there is a differential effect of number of separators on pain levels. Date and time of separator placement were also recorded. Within 5 minutes

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<sup>1</sup> Radio Opaque Blue Separators, Item #854-250 (lot #802699), American Orthodontics, 1714 Cambridge Avenue, Sheboygan, Wisconsin, 53082.



after separator placement subjects completed another VAS form identical to the pre-treatment form. At the end of the appointment, subjects were given verbal instructions on completing the study, a packet with an instruction sheet, a second dose (2 tablets) of their assigned drug to be taken 6 hours after the initial dose (5 hours after separator placement), 1 self-addressed stamped envelope and 4 color coded VAS forms to complete at 2 hours post-placement, 6 hours post-placement, bedtime, and 24 hours post-separator placement.

Questionnaire forms were color coded to permit validation of the evaluation period: yellow at two hours, orange at 6 hours, blue at bedtime, and pink at 24 hours. Subjects were asked to record when the second dose was administered. Completed forms were returned to the investigator in the self-addressed stamped envelope following completion of the 24-hour study.

During the 24-hour study, subjects were discouraged from taking additional medication and were advised against eating sticky foods that might dislodge the separators. If additional medication was consumed, the subjects were asked to write down the date, time, and type of medication taken. They were asked to contact the investigator if there were any future questions or adverse reactions.

### Sample Size

A power analysis was conducted to determine the sample size required to provide sufficient power to detect a statistically significant difference between placebo, acetaminophen and ibuprofen. The power analysis assumed an  $\alpha = 0.05$  and  $\beta = 0.20$ . Effect sizes estimates from Steen Law and others (2000) were used for computing sample size. Based on this analysis, a sample size of 28 per group was determined to be sufficient,

resulting in a total of 84 subjects. To account for a potential attrition rate of 10%, a total sample of 93 was planned for randomization into the 3 groups in the study. However, since there were no data on which to assess the relative effectiveness between ibuprofen and acetaminophen, an interim analysis was planned mid-way through the study to determine if power was sufficient to detect changes if any occurred between the two test groups.

#### Instrumentation and Measurement

Pain experience felt when teeth were not touching, during chewing, and when biting were assessed using visual analogue scales at each of the six time periods. The Visual Analogue Scale (VAS) is the accepted method for assessing orthodontic pain levels and has been used in numerous clinical trials to evaluate change in individual pain over time (Seymour et al. 1983; Ngan et al. 1989; Wilson et al. 1989; Jones and Chan 1992; Ngan et al. 1994; Scheurer et al. 1996; Steen Law et al. 2000; Bernhardt et al. 2001; Gould et al. 2001; Bergius et al. 2002; Erdinc and Dincer 2004; Bird et al. 2007; Bradley et al. 2007; Minor et al. 2009; Salmassian et al. 2009). The VAS is a line that measures 10 cm (100 mm) in length, with one end defined as “no pain” and the other end defined as “worst pain imaginable” with corresponding happy and unhappy faces. Subjects are asked to mark a point on the line corresponding to the level of perceived pain at that moment. The investigator then measures the distance from the lower end of the scale (0 mm) to the subject’s mark to measure pain intensity (Melzack 1975).

The questionnaires given to each subject were comprised of 3 horizontal VAS lines that individually assessed perceived pain under 3 conditions: when teeth were not touching, while chewing food, and when biting back teeth together (Appendix 1). Subjects were given

color coded, but otherwise identical VAS forms to complete at each of the six time intervals: immediately prior to separator placement, immediately following separator placement, 2 hours post-placement, 6 hours post-placement, bedtime and 24 hours post-placement. Subjects were asked to return their VAS questionnaires upon completion of the study in the pre-paid, self-addressed envelope given to them at their separator appointment. Upon receipt of the VAS questionnaires, a single investigator (S.K.) conducted all VAS measurements using a digital caliper. Intra-examiner reliability was assessed by a repeat measuring of all VAS data, one week after the initial measurements were performed. All repeat measurements were within 0.1 mm of the original measurements so examiner reliability was determined to be excellent.

#### Data Analysis

Data were analyzed using descriptive statistics and repeated measures ANOVA with treatment and time treated as fixed effects using SPSS (version 17.0)<sup>2</sup>.

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<sup>2</sup>. IBM SPSS Statistics, IBM Corporation, Route 100, Somers, New York 10589.

## CHAPTER 3

### RESULTS

In total, 9 males and 17 females completed the study prior to the interim analysis. Nine subjects failed to return data and were excluded. Table 1 shows demographic distributions across the three treatment groups. In the placebo group, 56% were male and 44% were female with a mean (SD) age of 12.6 (1.8). In the acetaminophen group, 30% were male and 70% were female with a mean age of 13.0 (1.6). In the ibuprofen group, 14% were male and 86% were female with a mean age of 12.7 (1.3). These percentages are typical of those who seek orthodontic treatment.

At the interim analysis, possible confounding effects (differences in pain scores under the 3 conditions) were explored as a function of age, gender or office from which subjects were recruited. As none of these variables were determined to be significant confounders, they were subsequently eliminated from future analyses. Evaluation of the relationship between number of spacers placed at initial treatment and the three pain perception measures over time showed that Pearson correlation coefficients ranged from  $r = 0.13$  to  $0.42$  suggesting little variance (0.02 to 0.18) in VAS pain scores was related to number of spacers.

As pain perception was measured at 6 time intervals clustered within patient, a repeated measures ANOVA was used for the interim analysis to assess effect of drug on pain over time and obtain effect size estimates (eta squared values). Results showed that there was no statistically significant effect ( $p > .05$ ) of group (treatment) or group by time interaction on pain as measured by the three VAS scales; however, there was a significant

increase in pain over time across all treatment groups ( $p < .001$ ) for each of the three conditions (Tables 2 and 3).

TABLE 1  
SUBJECT DEMOGRAPHIC DATA

	Avicel placebo (N=9)	Acetaminophen (N=10)	Ibuprofen (N=7)
Dosage	640 mg	650 mg	400 mg
Age: Mean (SD) Range	12.6 (1.8) 11-16	13.0 (1.6) 11-16	12.7 (1.3) 11-15
Female (%)	4 (44%)	7 (70%)	6 (86%)
Male (%)	5 (56%)	3 (30%)	1 (14%)
Separators: Mean (SD) Range	5.2 (2.3) 2-8	7.2 (1.1) 5-8	6.1 (2.0) 3-8

TABLE 2

MEAN PAIN SCORES (IN MILLIMETERS) OVER TIME UNDER  
THREE ASSESSMENT CONDITIONS

Analgesic		Time (Relative to separator placement)	Mean Pain mm (SD)  Teeth Not Touching	Mean Pain mm (SD)  Chewing	Mean Pain mm (SD)  Biting back teeth together
Group 1	Avicel placebo 640 mg	Immediately before	11.1 (27.3)	2.0 (4.2)	11.1 (19.2)
		Immediately after	25.8 (32.2)	20.3 (24.2)	36.8 (29.3)
		2 hours after	9.3 (10.5)	34.3 (33.3)	39.4 (33.6)
		6 hours after	44.6 (41.2)	50.2 (40.4)	52.2 (39.0)
		Bedtime	40.3 (40.2)	54.3 (43.2)	53.1 (42.2)
		24 hours after	34.3 (36.7)	65.6 (36.1)	70.9 (30.4)
Group 2	Acetaminophen 650 mg	Immediately before	1.5 (2.0)	2.1 (2.6)	1.7 (2.4)
		Immediately after	32.7 (27.1)	30.6 (37.2)	36.5 (39.1)
		2 hours after	14.5 (25.8)	27.1 (33.9)	23.7 (35.1)
		6 hours after	22.8 (34.1)	49.1 (35.7)	55.8 (33.2)
		Bedtime	29.4 (33.3)	53.1 (28.8)	52.1 (25.9)
		24 hours after	38.6 (38.7)	64.0 (30.9)	68.0 (30.1)
Group 3	Ibuprofen 400 mg	Immediately before	2.1 (2.0)	2.3 (2.1)	2.4 (2.0)
		Immediately after	23.3 (17.1)	32.9 (27.6)	41.4 (32.3)
		2 hours after	15.0 (12.2)	26.7 (18.6)	20.9 (21.9)
		6 hours after	24.6 (14.8)	37.3 (26.7)	43.1 (28.6)
		Bedtime	32.9 (27.8)	47.7 (26.8)	49.9 (29.0)
		24 hours after	39.1 (34.4)	52.6 (33.0)	55.1 (31.0)

TABLE 3

REPEATED MEASURES ANOVA SIGNIFICANCE AND ETA SQUARED VALUES  
UNDER THREE ASSESSMENT CONDITIONS

SOURCE	ANOVA RESULTS	Teeth Not Touching	Chewing	Biting Back Teeth Together
Group X Time	Sig.	.746	.926	.882
	$\eta^2$	.055	.037	.042
Group	Sig.	.853	.898	.764
	$\eta^2$	.014	.009	.023
Time	Sig.	.0001*	.0001*	.0001*
	$\eta^2$	.249	.491	.507

\*Statistically significant alpha = .05.



It was hypothesized that there would be a significant difference in pain as measured by VAS under the three assessment conditions over time and that the effect would differ between acetaminophen, ibuprofen and placebo. ANOVA analysis (Table 3) revealed that there was no statistically significant ( $p > .05$ ) interaction effect in pain levels as a function of group (treatment) over time for any of the three conditions: teeth not touching ( $p = .746$ ,  $\eta^2 = .055$ ); chewing ( $p = .926$ ,  $\eta^2 = .037$ ); and biting back teeth together ( $p = .882$ ,  $\eta^2 = .042$ ). The eta squared values for the three interaction effects suggests that little variance in pain (all less than 6%) is explained by the differential effect of group over time. There was also no statistically significant main effect of group on pain levels ( $p > .05$ ) for all three conditions: teeth not touching ( $p = .853$ ,  $\eta^2 = .014$ ); chewing ( $p = .898$ ,  $\eta^2 = .009$ ); and biting back teeth together ( $p = .764$ ,  $\eta^2 = .023$ ). As with the interaction effect, the eta squared values were minimal suggesting that the variance in pain levels is not closely related to differential effect of medications. However, the main effect of time on pain levels was found to be significant ( $p < .05$ ) for all three conditions (Fig. 2-4): teeth not touching ( $p = .000$ ,  $\eta^2 = .249$ ); chewing ( $p = .000$ ,  $\eta^2 = .491$ ); and biting back teeth together ( $p = .000$ ,  $\eta^2 = .507$ ). Post hoc pairwise comparisons at .01 level showed that pain at bedtime and at 24 hours were significantly greater than pretreatment for teeth not touching. For chewing, pretreatment was significantly less than all other time periods, but there was no difference in pain between time intervals once spacers were placed. The same trend was observed for biting on back teeth. The relatively large eta squared values suggest that a large proportion of variance in pain levels can be explained by time.

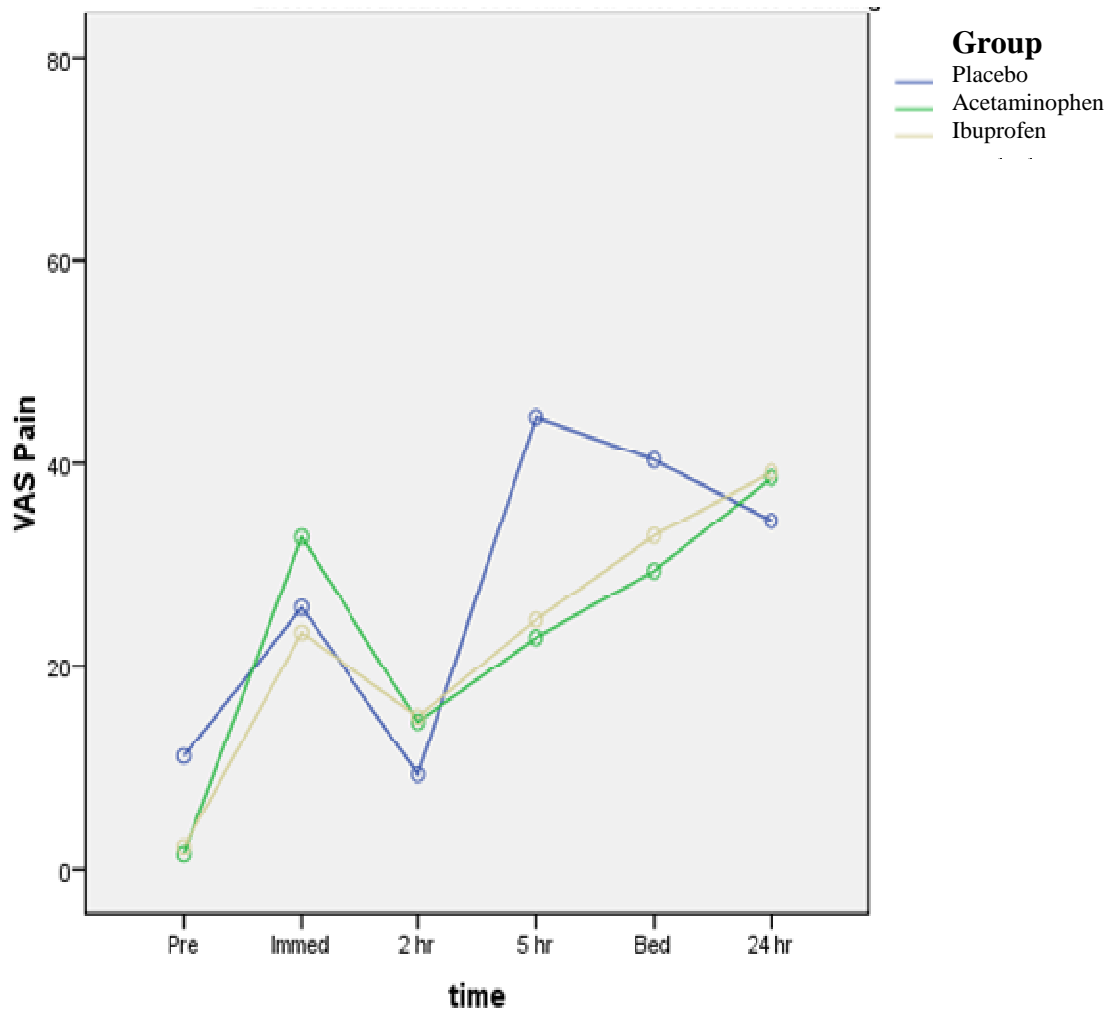


Fig. 2. Mean VAS pain levels over time by group when “teeth are not touching”.

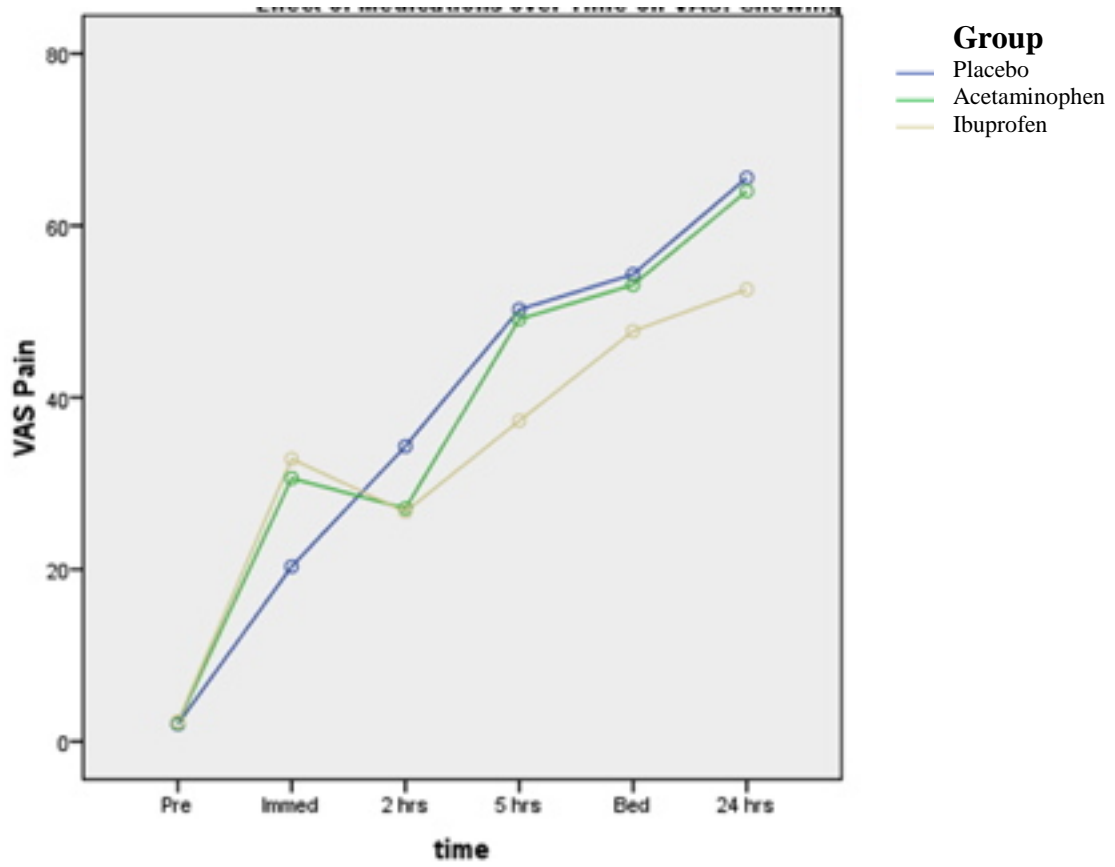


Fig. 3. Mean VAS pain levels over time by group when "chewing".

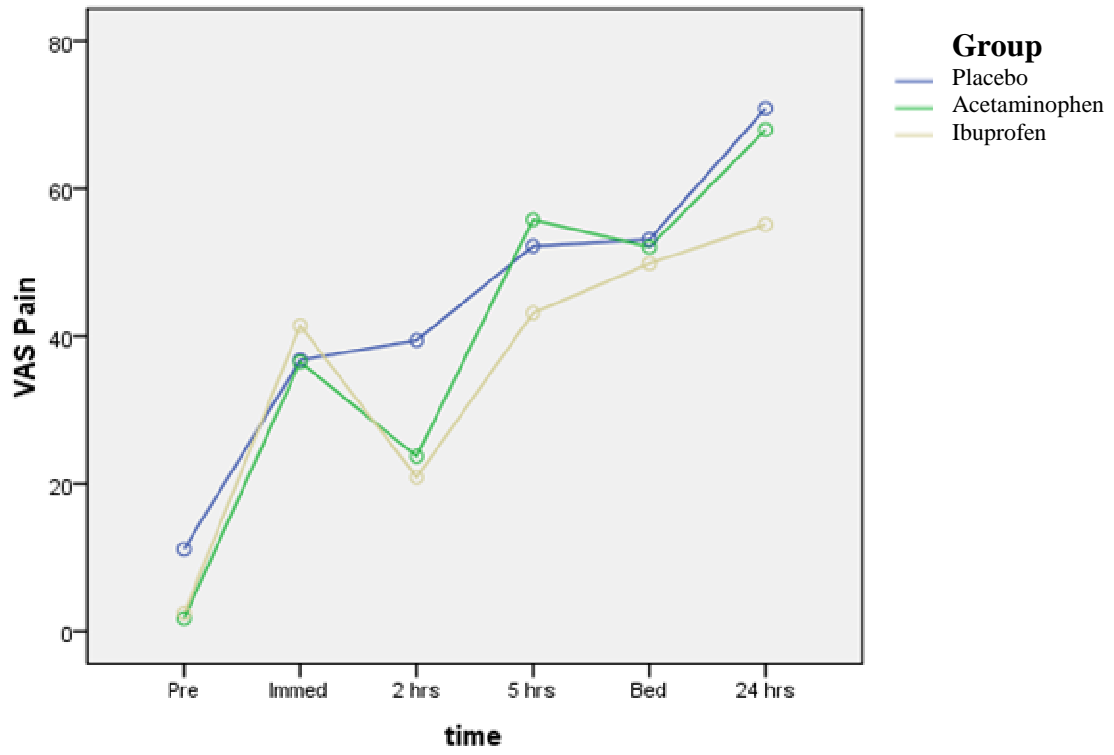


Fig. 4. Mean VAS pain levels over time by group when "biting back teeth together".

## CHAPTER 4

### DISCUSSION

The aim of this study was to compare pain control effectiveness of a combined regimen of preemptive and postoperative acetaminophen, ibuprofen, and placebo therapy during three assessment conditions over time following orthodontic separator placement. It was hypothesized that there would be a significant difference in pain over time as measured by visual analogue scales (VAS) between the two analgesics, acetaminophen and ibuprofen.

At the interim analysis, data were evaluated to obtain effect size measures to determine if the original subject recruitment plan and sample size were sufficient to detect a difference if one existed. The analysis showed that pain was highly variable within group as well as between groups, irrespective of drug (group) assignment. As a result of the highly variable pain scores and small effect sizes (.01 for group and .03 for time\*group), it was determined that the power calculations based on estimates by Steen Law and others (2000) were inaccurate for this population. The estimates provided by the Steen Law study were based on data collected from pain control assessments using a single drug (ibuprofen), rather than a comparison of ibuprofen and acetaminophen. Furthermore, subjects participating in the Steen Law study were patients from the clinical pool of the University of Iowa College of Dentistry's Department of Orthodontics with a maximum age of 16 years whereas our sample originated from two private orthodontic offices in Lee's Summit, Missouri, with an age range between 9 and 17 years. Owing to the differences in effect size estimates between our study and the Steen Law study, and restricted access to the sample size needed to show statistically significant differences, it was agreed to stop the trial following the interim

analysis. In order to sufficiently power the study, an unobtainable sample size would be required; therefore, the study was concluded.

RM ANOVA data for all three treatment groups, acetaminophen, ibuprofen, and placebo, show a trend for pain levels to increase immediately after separator placement, decline to the 2 hour time period, then gradually increase to the 24 hour time period. Time proved to be the only significant factor accounting for variability in pain, while there was no significant main effect of group or interaction effect between group and time (Table 3). Of particular note is the considerable within group variance in pain scores found for the three VAS conditions over time, particularly in the later time intervals, suggesting that pain perception is highly subjective and differs between subjects. The variance between groups is concealed by the high variance within groups.

Pain was evaluated by VAS measurements during three conditions in this study: when teeth were not touching, while chewing food, and when biting back teeth together (Appendix 1). In all three conditions, a positive correlation was present between pain levels and time; low correlation when teeth were not touching and moderate correlations when chewing and biting back teeth together. Pain scores reported when teeth were not touching (therefore not in function) were lower than scores reported when teeth were in function, when chewing or biting back teeth together. Teeth subjected to insult by separators and the subsequent inflammatory process would experience increased movement in function (chewing and biting). Further compression of the periodontal ligament and deformation of mechanical pressure receptors result in an enhanced inflammatory response and higher pain scores. Descriptive examination of trend lines exhibit similar patterns of pain over time between the

three conditions varying only in magnitude of pain, with the lowest magnitude when teeth were not touching and higher magnitudes when teeth were in function. Trend lines for chewing and biting back teeth together suggest that ibuprofen provided slightly better, albeit non-significant, pain control followed by acetaminophen, however neither were statistically more effective than the placebo.

To date, only two studies have compared acetaminophen and ibuprofen preemptively for pain associated with orthodontic separator placement (Bird et al. 2007; Bradley et al. 2007). The study by Bird and others (2007) utilized similar subject inclusion criteria and methodology and found comparable pain fluctuation trends and reached similar conclusions. The study also compared pain levels during three different conditions: when teeth were not touching, when chewing, and when biting back teeth together. General pain pattern fluctuations for all three conditions mirrored those found in our study with the magnitude of pain levels also higher when teeth were in function. However, in contrast to Bird's study we incorporated a second analgesic dose 6 hours after the initial dose for the purpose of extending pain control. The second dose did not significantly reduce delayed pain, therefore our conclusion simply paralleled that of Bird and others that there was no significant difference in orthodontic separator pain control between acetaminophen and ibuprofen.

Bradley and others (2007) also incorporated a second analgesic dose, comparing preemptive and postoperative ibuprofen and paracetamol (acetaminophen) and attained descriptive results similar to those found in this study; however, they employed a different approach to assess pain efficacy. Subjects were instructed to consume their assigned medication 1 hour prior to separator placement and a second dose 6 hours after placement.

Unlike our 6-hour dosing interval, this dosing interval of 7 hours exceeds the 4-6 hour duration of action of both analgesics. In contrast to our hypothesis that there would be a significant difference in pain control between ibuprofen and acetaminophen, they were able to determine statistical improvement of ibuprofen over acetaminophen using a non-inferiority (equivalence) approach. Using a non-inferiority margin of  $\pm 10$ mm on the VAS scale, they determined that the mean difference in pain scores fell in the equivalent margin, however the right end of the 90% confidence interval crossed over the +10 margin of equivalence resulting in the conclusion that acetaminophen is not equivalent to ibuprofen in pain control. They therefore concluded that ibuprofen was superior.

A potential reason for the significance in the study by Bradley and others (2007) might be due to a lack of baseline pain measurement. As pain is a subjective phenomenon, individual variation of pain tolerance and pain perception is inevitable. The first pain level recorded on VAS was 2 hours after separator placement and a placebo group was not included as a baseline for comparison. Without a true baseline (pre-treatment) measurement and control group, it is not possible to determine whether initial pain levels were comparable between groups. If higher inherent pain tolerance was present in the ibuprofen group, a conclusion that ibuprofen is more effective than paracetamol might be faulty. It is also important to note that they combined all pain measures after the 2-hour observation (2, 6, bedtime, 24 hours, 3 days and 7 days post separator) into a single mean score for group comparison.

In the current study, potential reasons for lack of statistical difference between the three treatment groups might include the highly subjective and variable nature of pain,



inadequate analgesic dosage amounts, an inappropriate dosage strategy, and/or small sample size. The subjective nature of pain can create difficulty in accurately capturing change in pain over time. Opposite to what would be expected, some subjects felt little to no pain even though they were in the placebo group, while some of the subjects in an analgesic group reported high levels of pain.

The standard analgesic dosages utilized in this study may have been too low to result in an effect great enough to counteract orthodontic pain and reveal the difference in pain effectiveness between analgesics. Bird and others (2007) utilized identical treatment dosages as in our study and also found no significant difference in pain control between acetaminophen and ibuprofen. Bradley and others (2007) administered an identical amount of ibuprofen (400 mg), but incorporated a higher dose of paracetamol (1 g) compared to the 650 mg utilized in our study. They concluded a statistical improvement of ibuprofen over acetaminophen in pain control however no true baseline measurement or control group was incorporated into the study.

Dosing strategy timing can be re-arranged where the second dose might be given earlier, at 4 or 5 hours after the first dose, allowing for earlier onset and more analgesic to be present in the system. This multiple dose study incorporated a preemptive and postoperative dose of medication. To date there are no studies comparing multiple analgesics on effectiveness of orthodontic separator pain control with a three dose analgesic regimen.

Lastly, our small sample size and small effect sizes clearly resulted in non-significant findings. The eta squared values which give an estimate of effect size (not dependent on sample size) suggests that the effect of medications as administered in this study were small.

It is likely that extending the analgesic medications beyond the initial 24-hour period may result in a greater effect size and future studies are needed to assess this hypothesis.

During tooth movement, mild inflammation occurs with vascular compression leading to the release of prostaglandins that aid in the dissemination of pain (Furstman and Bernick 1972; Ferreira et al. 1978; Saito et al. 1991; Proffit and Fields 2000). If prostaglandins and the inflammatory process are the cause for pain levels during orthodontic treatment it would seem appropriate that extended ibuprofen dosing, with analgesic, antipyretic, and anti-inflammatory properties would be the drug of choice in comparison to acetaminophen which is not by definition an anti-inflammatory analgesic. However, similar to the study by Bird and others (2007), our study showed that both ibuprofen and acetaminophen proved to have similar outcomes in pain control which leads us to conclude that it is the analgesic, rather than anti-inflammatory effect that is the chief mode of action for orthodontic pain relief.

The use of a placebo or control group in this study was incorporated to provide a baseline for comparison to determine the true effect of the studied analgesics on pain control. Although there was no statistically significant difference in pain control between all three groups, there was a trend for the placebo group to experience slightly higher scores after the 2-hour assessment period during chewing and biting (Fig. 3-4). These results coincide with our expectation that both acetaminophen and ibuprofen analgesics provide some level of pain relief during orthodontic treatment, although not at statistically significant levels. Pain continued to persist through the 24 hour time period, therefore we can conclude that two analgesic doses (of either 400 mg ibuprofen or 650 mg acetaminophen), given 1 hour before

separator placement and 6 hours later, does not provide adequate pain control and a more effective long-term pain control regimen needs to be developed and evaluated.

Subjects in our study received orthodontic separators between posterior teeth to create space by pushing teeth apart for subsequent placement of orthodontic bands. Numbers of separators ranged from 2 to 8 per individual. By group, the acetaminophen group had the greatest mean number of separators of 7.2, followed by the ibuprofen group at a mean of 6.1, and the placebo group at 5.2. Currently there are no published studies that compare number of orthodontic separators on pain levels. It seems feasible to assume that a positive correlation would exist between number of separators and degree of pain; however, in this study, Pearson correlation coefficients between number of separators and all VAS pain measurements ranged from  $r = 0.13$  to  $0.42$  suggesting that only mild variance in pain scores over time were related to number of spacers. It is therefore clear that other factors are involved in variation in pain perception.

Pain experience as a result of orthodontic separator placement and resultant tooth movement is a common phenomenon that concerns patients and clinicians. This study agrees with former studies that delayed pain continues to increase at a gradual rate throughout the 24-hour period following separator placement (Ngan et al. 1994; Steen Law et al. 2000; Bernhardt et al. 2001; Bird et al. 2007; Bradley et al. 2007). However in contrast to those studies which started measurements after separators were placed, the current study and that of Bird and others (2007) incorporated a pre-treatment baseline VAS measurement that revealed the immediate increase in pain level following separator placement and the subsequent reduction in pain level through the 2 hour time period. Earlier studies started

pain measurement no earlier than 2 hours after separator placement so this preemptive effect on immediate pain was not noted.

More investigators have started to compare preemptive and postoperative analgesics in hopes to provide longer lasting effective pain control in orthodontics (Steen Law et al. 2000; Bernhardt et al. 2001; Bird et al. 2007; Bradley et al. 2007; Minor et al. 2009). Steen Law and others (2000) and Bernhardt and others (2001) found that subjects receiving preemptive ibuprofen reported significantly lower pain levels 2 hours after separator placement compared to the subjects receiving only postoperative ibuprofen. The combination of a preemptive and postoperative dose in the Bernhardt study did not produce significantly more pain control within the 24-hour period over the subjects who received only a single preemptive ibuprofen dose. Of interest, Minor and others (2009) performed a single analgesic (ibuprofen) study that investigated the effect of incorporating a third 400 mg dose of ibuprofen 7 hours after separator placement. Unlike our study, Minor was able to evaluate the effect of preemptive ibuprofen versus the lack of a preemptive dose. Group 1 was given three dosages of ibuprofen (1 hour prior to separator placement and 3 and 7 hours after placement), group 2 received preemptive placebo then two postoperative dosages of ibuprofen, and group 3 was given three placebo dosages. Group 1 experienced significantly less pain at 6 hours, at bedtime, and on the following morning after separator placement and no difference was found between groups 2 and 3. This suggests that in regards to immediate (early) pain control, there appears to be no advantage to the use of preemptive ibuprofen. However, due to the significant reduction in pain at 6 hours, bedtime, and on the next morning, preemptive ibuprofen accompanied by a multiple dose regimen (in this case given

at 3 hours and 7 hours post placement) may play a key role in controlling the delayed pain response.

The current study found that preemptive analgesia tended to decrease pain levels at the 2 hours time point, however this was not statistically significant, and found a lack of pain reducing effect from the postoperative dose as pain continued to increase through the 24-hour period. These results suggest a possible benefit of preemptive analgesia in reducing pain within the first 24 hours but a lack of evidence to support the use of a postoperative dose to lengthen the effect. General trend of pain appeared to peak at the time of separator placement and at 24 hours similar to previous studies (Steen Law et al. 2000; Bernhardt et al. 2001; Bird et al. 2007). Subjects in the acetaminophen and ibuprofen groups experienced similar levels of pain, while there was a trend for higher pain levels in the placebo group after the 2-hour assessment, however this was not statistically significant.

Gender differences in the orthodontic pain experience are a subject of debate. It was historically felt that females tend to have an increased sensitivity to pain and are therefore less pain tolerant than men (Bergius et al. 2000), with some studies concluding that females perceive pain to a greater extent than men and attribute this difference to genetics, variation in hormones, and social and psychological factors (McGrath and Craig 1989; Scheurer et al. 1996; Keogh and Herdenfeldt 2002). Other studies of orthodontic pain, this study found no gender differences in orthodontic pain intensity or prevalence (Ngan et al. 1989; Jones and Chan 1992; Erdinc and Dincer 2004; Minor et al. 2009; Salmassian et al. 2009). Our study found no significant differences in pain perception between male and female subjects. A possible explanation could be due to cognitive factors such as motivation and expectation,

which are encountered more than emotions of anxiety and fear in the orthodontic setting. Orthodontic patients, unlike dental patients, are motivated towards treatment, with a goal of better function and esthetics. These factors act as filters on perception, judgment, and pain perception and therefore play a strong role in the success of orthodontic treatment (Bergius et al. 2000).

Studies of the relationship between age and pain threshold have been conducted and it is still unclear whether age has an influence on pain threshold or pain tolerance. Tucker and others (1989) reported that cutaneous pain threshold increases with age. Up to age twenty-five a rapid increase in pain threshold occurred followed by a plateau and gradual rise until the age of seventy-five where there was another rapid threshold increase (Tucker et al. 1989). It is much more difficult to determine the relationship of age to pain perception in orthodontic patients, probably since treatment plans can differ based on the age of the patient. Similar to other studies, this study did not find significant differences between age and degree of orthodontic pain threshold, however our age inclusion criteria was limited to 9-17 years of age, with actual participants ranging between 11-16 years of age. If our study was conducted with a larger age range, age-related effects might have been observed.

Out of 26 subjects, only one subject required additional medication. A 12-year old female randomly assigned to the placebo group, consumed two additional tablets of ibuprofen the morning after separator placement, 16 hours after the initial dose. Despite the fact that she was only given preemptive and postoperative placebo, she was able to refrain from taking additional medication until the next morning suggesting a high pain tolerance, or perhaps a strong willingness to adhere to research protocol.

It is apparent that further studies need to be conducted to determine an analgesic regimen effective for complete control of pain induced by orthodontic separator placement. Past studies have demonstrate the possible benefit of using preemptive analgesia to reduce immediate discomfort however the method to control delayed pain needs further investigation (Steen Law et al. 2000; Bernhardt et al. 2001; Bird et al. 2007; Bradley et al. 2007; Minor et al. 2009). In this study VAS data collected from subjects receiving separators at two orthodontic offices varied widely in magnitude irrespective of treatment group. This individual variability, which seems to be unrelated to age, gender or number of separators, can only be attributed to the inherent characteristics of the subjects in this study and the subjectivity of the pain experience. Within each subject we have potential differences in pain perception, pain threshold/tolerance, medication susceptibility/sensitivity, and emotional considerations such as dental anxiety or dental fear. Although variations in magnitude were evident between treatment groups, the general trend lines were similar, with pain increasing immediately after separator placement, declining to the 2 hour time period, and then gradually increasing to the 24 hour time period. Although not significant, ibuprofen appeared to provide slightly better pain control than acetaminophen, however neither were significantly more effective than the placebo.

Until further investigation yields an effective standard method for the control of immediate and delayed orthodontic separator pain, orthodontists can recommend preemptive acetaminophen or ibuprofen 1 hour prior to separator placement to aid in the control of immediate discomfort. If there is concern regarding the potential decrease in rate of tooth movement with ibuprofen, or if ibuprofen is contraindicated, acetaminophen would the

appropriate recommendation. Although individual variation will ultimately affect the amount and duration of pain experienced, all patients should be informed about possible latent discomfort and briefed on acceptable adjustments in dosage amounts or timing of dosages according to medication manufacturer recommendations.

### Study Limitations

It has been found that pain from separator placement exceeds the duration of our study timeline of 24 hours. Therefore, it would be advantageous to determine a more effective analgesic regimen for more long-term effective pain control, whether by utilizing different medications, adjusting dosage amounts or dosage timing, or increasing the number of dosages.

All subjects were recruited from two orthodontic offices in middle to upper class neighborhoods in Lee's Summit, Missouri, therefore results from this study can be only be generalized to areas with similar characteristics.

A particular challenge to this study was the difficulty of subject recruitment from multiple offices. This proved to be difficult in part due to the availability and time for recruitment and parent's consideration of the possibility that their child would be randomly assigned to a placebo group who would not receive analgesics following separator placement. These factors made it difficult for subject recruitment and resulted in a fairly small sample size. It should be noted that our small sample size increases the risk of type II errors in which a conclusion of no effect is made when an effect is actually present. However, the small effect size lessens the degree to which this threat is present in making



statistical conclusions. Irrespective, given the small sample, results from this study should be cautiously interpreted.

#### Future Recommendations

Since ibuprofen and acetaminophen have pain control properties that are well tolerated by orthodontic patients, future research should focus on determining a more effective multiple dose protocol that will enable pain to be adequately controlled for a longer period of time. This might include testing new medications, increasing administered dosage amounts, increasing the number of dosages, or shortening time periods between dosages. To lengthen the analgesic effect of acetaminophen and ibuprofen, studies should evaluate whether these medications need to be taken at a shorter intervals or with increased dosages. For example, studies can attempt to adjust dosages to 1000 mg acetaminophen every 4 hours or 800 mg ibuprofen every 6 hours. Alternative analgesics should also be investigated.

According to a study by Arias and Marquez-Orozco (2006), ibuprofen significantly reduced the number of resorption lacunae and osteoclasts in pressure areas of orthodontic tooth movement in Wistar rats, and resulted in less tooth movement in comparison to acetaminophen. Acetaminophen demonstrated results similar to the control group. If both medications provide similar pain control levels and there is potential for ibuprofen to cause a delay in orthodontic tooth movement, orthodontists should consider recommending acetaminophen to their patients to minimize discomfort.

Orthodontists are aware that their patients will experience some degree of pain with tooth movement by separators or fixed orthodontic appliances. Although more research is needed to determine the most effective type of medication, dosage, and timing of delivery,

either acetaminophen or ibuprofen can be recommended preemptively to lessen the early discomfort that is expected following orthodontic separator placement.

## CHAPTER 5

### CONCLUSIONS

The purpose of this randomized, double blind, prospective clinical study was to compare the pain control effectiveness of preemptive and postoperative acetaminophen and ibuprofen compared to placebo therapy following separator placement. The following conclusions were made:

1. No significant difference in pain was found between the three groups, acetaminophen, ibuprofen and placebo, over the 24-hour study period.
2. No significant group (treatment) effect was found between acetaminophen, ibuprofen and placebo groups on pain levels, irrespective of time.
3. Significant differences in pain were found over time, irrespective of group. In general, pain tended to decrease into the second hour after separator placement then gradually increased up to the 24 hour time period. Ibuprofen and acetaminophen taken 1 hour prior to orthodontic separator placement are equally effective in decreasing immediate pain levels, however this was not statistically significant.
4. In all groups, pain peaked at 2 hours and 24 hours after separator placement.

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APPENDIX 1  
VAS QUESTIONNAIRE



Visual Analogue Scale Questionnaire

Current Date: \_\_\_\_\_



Current Time: \_\_\_\_\_

Please help your child to make ONE small vertical mark on each line below to indicate how their teeth feel when:

TEETH ARE NOT TOUCHING

No Pain \_\_\_\_\_ Worst Pain Imaginable  
 

CHEWING

No Pain \_\_\_\_\_ Worst Pain Imaginable  
 

BITING BACK TEETH TOGETHER

No Pain \_\_\_\_\_ Worst Pain Imaginable  
 

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