An Evaluation of Intranasal Ketorolac in an Untreated Endodontic Pain Model

A Thesis

Presented in Partial Fulfillment of the Requirements for

the Degree of Master of Science in the

Graduate School of The Ohio State University

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2018

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Abstract

Introduction: Previously, ketorolac was available for primary use only via intravenous and intramuscular routes. Its availability in intranasal form offers an alternative route of administration that patients can self-administer. The purpose of this study was to compare the efficacy of intranasal ketorolac (Sprix®) to a combination of ibuprofen/acetaminophen in an acute pain model of untreated endodontic patients experiencing moderate to severe pain and symptomatic apical periodontitis.

Methods and Materials: Seventy patients experiencing moderate to severe pain, a pulpal diagnosis of symptomatic irreversible pulpitis or symptomatic necrosis, and a periapical diagnosis of symptomatic apical periodontitis participated. Patients were randomly divided into two groups and received either 31.5 mg intranasal ketorolac and placebo capsules (n=36) or 1000 mg acetaminophen/600 mg ibuprofen capsules and a mock nasal spray (n=34). Patients recorded perceived pain scores on a VAS every 15 minutes for 240 minutes. Time to 50% pain relief, time to first sign of pain relief, and to meaningful pain relief were recorded and the data analyzed.

Results: A decline in reported pain was observed until 120 minutes post-dosing, after which reported pain remained relatively constant. Fifty percent pain relief was achieved at 70 minutes and 87 minutes for the acetaminophen/ibuprofen/mock nasal spray group

and placebo/intranasal ketorolac group, respectively, with no significant difference between the groups.

Conclusions: The effectiveness of intranasal ketorolac was not significantly different from that of a 1000 mg acetaminophen/600 mg ibuprofen combination. Intranasal ketorolac provides a non-narcotic alternative and an additional route of medication administration to practicing clinicians.

DEDICATION

To Shea. There will never be words to express my gratitude for our partnership in this life, but know that I am so thankful for the gift of your empowering, persistent love.

ACKNOWLEDGMENTS

Thank you to Dr. Drum for your example of a strong woman of integrity who leads with just the right proportion of firmness and love. You have been an inspiration and role model to me throughout residency. I hope to one day be half the woman you are.

Thank you to Dr. Reader whose tough questions followed by your unmistakable grin never fail to warm the soul. Your brilliance and wit are the essence of Ohio State Endodontics.

Thank you to Dr. Nusstein who so patiently explains how to approach difficult clinical situations and dedicates hundreds of hours to maintain our program as one of the best in the country. I will never see a squirrel without thinking of you.

Thank you to Dr. Fowler whose quiet nature and gentle spirit belie an incredibly brave woman who has dedicated her life to bettering the futures of not only her biological children, but also the futures of her dental student children. It has been a pleasure to share a love of cats (well, all animals really), Disney, and strong female authors/speakers with you.

Most of all, thank you all for not only being completely invested in making us the best clinicians possible, but also for teaching us to being better humans. I have truly felt the strength of our program's unique "endo family" dynamic, and now carry its responsibility into practice. The world is a better place as a result of your selfless contributions.

Last, but certainly not least, to Steve, Jeremy, and Jake. I can't imagine a better team with which to journey through residency. You are all kind, genuine people that I love like family. I'll miss our daily chats, case discussions, and laughs, but I am so looking forward to seeing where the future takes us all. I know our group chat will live on and distance won't keep us apart!

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Chapter 1: Introduction

On May 22, 2018, the American Dental Association composed a letter to the Pain Management Best Practices Inter-Agency Task Force with the main criticism of the federal response to the opioid crisis being that federal agencies had not sufficiently addressed best practices for managing acute pain versus chronic pain (1). An additional criticism was that federal efforts had not sufficiently addressed best practices for managing postoperative dental pain, which is more nuanced than managing pain in medical settings (1). With the opioid crisis showing no signs of slowing and the lack of studies showing narcotics to be more effective at managing dental pain than non-steroidal anti-inflammatory drugs (NSAIDs) (2), the need for studies providing information on effective, non-narcotic management of acute dental pain of inflammatory origin (i.e. toothache) is clear.

Ketorolac is an NSAID that has been proven to have efficacy similar to opioids and is therefore indicated for use in the management of patients requiring pain relief at the opioid level (3-8). Previously, ketorolac was only available for use via intravenous (IV) or intramuscular (IM) administration. An oral form is available, but is only indicated for use as supplementation after IV or IM administration of ketorolac. Therefore, the development of this powerful NSAID in intranasal form has potentially important implications for preoperative at-home use and postoperative outpatient settings, as

required in endodontics. Ketorolac is the first, and likely only, NSAID to become available for effective intranasal administration due to its high water solubility (9). General advantages of an intranasal route of administration include: faster absorption time, lack of first-pass metabolism, faster time to pain relief, ease of use, patient tolerability, and ability of use when patient is nauseated (8, 10). The efficacy of intranasal ketorolac has been proven in medical and oral surgery models, but there are no studies: comparing intranasal ketorolac to another non-opioid pain medication, evaluating the efficacy of intranasal ketorolac in an endodontic model using the currently recommended dose amount and schedule, or evaluating the efficacy of intranasal ketorolac preoperatively for longer than 30 minutes post-dose (3, 5-8, 10).

Currently, a combination of acetaminophen and ibuprofen is recommended by many medical and oral surgery protocols for pain control (11-13). These non-endodontic models are the basis for our current postoperative therapy. However, a recent systematic review concluded that there is insufficient evidence to recommend the most effective NSAID, dose amount, or dose interval for endodontic patients experiencing postoperative pain (14). Additionally, studies in acute pain models in which the patient presents with no or minimal pain or studies of postoperative pain in third molar extraction models are very different than studying an endodontic model where patients present with moderate to severe pain and an untreated endodontic need.

Symptomatic apical periodontitis (which occurs as a result of the inflammatory pulpal conditions of symptomatic irreversible pulpitis and symptomatic necrosis) and the presence of preoperative pain have been found to be among the most significant

predictors of postoperative pain in an endodontic model (15). Studying the use of pain medication preoperatively in an endodontic model likely provides a more accurate representation of the medication's postoperative capabilities, as the efficacy of the drugs are studied without the confounding factor of treatment. In this way, one is able to observe the effect of the active drugs in a model where nothing has been done to alleviate the patient's discomfort other than administration of medication.

Therefore, the purpose of this study was to compare the efficacy of intranasal ketorolac (Sprix®) to a combination of ibuprofen/acetaminophen in an acute pain model of untreated patients experiencing moderate to severe pain, a pulpal diagnosis of symptomatic irreversible pulpitis or symptomatic necrosis, and a periapical diagnosis of symptomatic apical periodontitis.

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Chapter 2: Materials and Methods

Seventy adult emergency patients participated in this study. All participants were in good health (ASA Class I or II) as determined by a health history and verbal questioning. Exclusion criteria were as follows: subjects who were younger than 18 years and over 65 years; subjects who were less than 110 pounds in weight; unable to take or allergic to ketorolac, ibuprofen or acetaminophen; allergic to local anesthetics or sulfites; pregnant or nursing, history of significant medical problem (ASA class III or higher); angioedema or bronchospastic reactivity to aspirin or other NSAIDs; gastrointestinal problems; patients who had taken central nervous system depressants or any analgesic medication within the preceding 4-6 hours; or inability to give informed consent. The study was approved by The Ohio State University Human Subjects Review Committee, and written informed consent was obtained from each participant. All participants also completed a Health Insurance Portability and Accountability Act (HIPPA) research authorization form and a Corah dental anxiety scale to rate their level of anxiety (16).

To qualify for the study, each participant had a tooth with a periapical diagnosis of symptomatic apical periodontitis and a pulpal diagnosis of symptomatic irreversible pulpitis or symptomatic necrosis and was actively experiencing moderate to severe pain

at the time of the emergency visit. Symptomatic apical periodontitis was defined as a tooth exhibiting a painful response to biting, percussion, and/or palpation (17). Symptomatic irreversible pulpitis was defined as a tooth exhibiting prolonged response to cold testing with Endo-Ice® (1,1,1,2 tetrafluoroethane; Hygenic Corp, Akron, OH) and spontaneous pain upon presentation. Symptomatic necrosis was defined as a tooth exhibiting a negative response to an electric pulp tester (Analytic Technology Corp., Redmond, WA) and to Endo-Ice®, a periapical radiolucency on radiographic exam using periapical digital radiography, and spontaneous pain upon presentation. No patients had a draining sinus tract. Initial pain intensity (baseline pain score) was determined by a Heft-Parker visual analogue scale (VAS)(18) after the form was explained to the participant. The VAS is a 170 mm line that is divided into 4 categories. No pain corresponds to 0 mm. Mild pain is defined as greater than 0 mm and less than or equal to 54 mm. Mild pain includes the descriptors of "faint", "weak", and "mild" pain. Moderate pain is defined as greater than 54 mm and less than 114 mm and includes the descriptor "moderate." Severe pain is defined as equal to or greater than 114 mm. Severe pain includes the descriptors of "strong", "intense", and "maximum possible." The participant was instructed to mark the place on the VAS that correlated to the pain they were feeling at that moment. Only those participants that marked in the moderate to severe range were included in the study. Therefore, each patient that participated in the study was experiencing moderate to severe pain associated with a tooth that fulfilled the criteria for a periapical diagnosis of symptomatic apical periodontitis and a pulpal diagnosis of symptomatic irreversible pulpitis or pulpal necrosis.

The control drugs, acetaminophen/ibuprofen combination, were used as a comparator analgesic because there is some evidence of its efficacy in an acute pain model of untreated pain of endodontic origin with moderate to severe pain at the time of treatment. (19-21). The pain participants were experiencing was severe enough that a placebo group was not clinically warranted.

Each participant was randomly assigned to receive either one dose of 1000 mg acetaminophen and 600 mg ibuprofen and a saline placebo nasal spray or placebo medication and 31.5 mg ketorolac (Sprix®; Egalet US Inc., Wayne, PA) nasal spray. The medications in each group were randomly assigned a six-digit number to blind the experiment using www.random.org. The random numbers were applied to all medications by a compounding pharmacist, in order to blind the investigator. The ibuprofen/acetaminophen and placebo medication were compounded by the compounding pharmacist to prevent identification of drug versus placebo as was done in previous investigations (22). The ibuprofen/acetaminophen and placebo medications were compounded into capsules of identical appearance and color. Each participant received either four acetaminophen/ibuprofen capsules or four placebo capsules, depending upon which group they were randomly assigned to. The components for the saline nasal spray and instructions for its assembly were provided by the same compounding pharmacist. The saline and Sprix® nasal spray bottles were wrapped with paper obscuring the labels to blind the participant and only identified by a random number. A trained research associate administered the appropriate medications labeled with the appropriate random number to the participant. Therefore, neither the participant

nor primary investigator was aware of which medication they received because only the random numbers identified the medications. The master list of six-digit random numbers was only available to the lead researcher; it was not available to the primary investigator until completion of the study.

The instructions given to the participant by the trained research assistant were as follows: The participant was seated in an operatory in the endodontic clinic at The Ohio State University College of Dentistry, where they remained for the duration of the study. The assistant opened the vial of capsules and handed it to the participant, along with a cup of water. The participant was instructed to take all the pills. Instruction for administration of the nasal spray were then given per manufacturer's instruction with special emphasis on ensuring the participant did not inhale the drug during administration (23). All patients were instructed to blow their nose prior to administration. In an effort to mimic at-home conditions, the assistant then instructed the patient on how to prime the bottle and administer the medication. Patients were told to prime the bottle by depressing the pump several times until a small amount of the medication was seen expressed from the bottle. For administration, the patients were told to tilt their head slightly down then insert the tip of the bottle away from the center of their nose directing the spray toward the outside of their nose. Then one spray was to be administered in each nostril. It was emphasized that patients were not to inhale the medication; it was meant to simply coat the inside of their nose. Patients then followed the instructions they were given and administered the medication themselves, as they would at home. After the administration of the medications, participants were asked to record any effects experienced during

medication administration on the data collection sheet they were provided. The primary investigator was not present in the room during medication administration and did not see the medication vials prior to or after their administration.

Immediately after the medication administration, the time of administration was recorded and a three-line timer (LCD 3-line Timer; Docooler Inc., City of Industry, CA) with all lines set at 4 hours (240 minutes) was started. Pain intensity scores were recorded every 15 minutes over 240 minutes using the aforementioned Heft-Parker VAS. The top line of the timer was used to assist the participant in marking their pain intensity every 15 minutes; therefore, the top-line time counted down throughout the entire study. The button to stop the middle line on the timer was marked in blue. The patient was instructed to stop the middle line on the timer by pressing the blue button when they first felt any pain relief and record the time displayed in the corresponding space on the data collection sheet they were provided. The button to stop the bottom line on the timer was marked in red. The participant was instructed to stop the bottom line of the timer by pressing the red button when they felt that the pain relief became meaningful to them (when they no longer focused on the pain) and record the time displayed in the corresponding space on the data collection sheet they were provided. Mean VAS scores were calculated for each time point in each group. As a secondary efficacy measure, using the scores provided on the Heft-Parker VAS, the 15-minute range during which the participant's pain relief reached equal to or greater than 50% (pain half gone) was calculated by the investigators.

Any adverse effects experienced by the participant during the study were recorded by a dedicated space inquiring if the participant was experiencing any other effects from the medications. If any effects were experienced, they were recorded by the participant in this space on the data collection sheet they were provided. At the conclusion of the study, participants were offered emergency root canal treatment at a time set with the provider and the participant according to the participant's schedule.

Data was collected and statistically analyzed. Comparisons between the acetaminophen and ibuprofen combination group and intranasal ketorolac group for age, weight, and presenting pain intensity were analyzed using the randomization test. The patients' Corah Dental Anxiety Scales were analyzed using the Wilcoxon Rank Sum Test. Sex was analyzed using the chi-squared test. Average pain as marked on a 170 mm VAS at each time period, Time to First Sign of Pain Relief, Time to Meaningful Pain Relief, and Time to 50% of Initial Pain was analyzed using ANOVA.

With a non-directional alpha risk of 0.05 and assuming a standard deviation of 48 (4), a sample size of 35 patients per group (for a total of 70 patients) was required to demonstrate a difference of ± 35 mm on a 170 mm VAS with a power of 0.85.

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Chapter 3: Results

Seventy subjects completed the study with 34 subjects randomly assigned to the acetaminophen/ibuprofen/mock nasal spray group and 36 to the placebo/intranasal ketorolac group. Table 1 shows the demographics of the subject population in each group by sex, age, weight, initial pain (as measured on a 170 mm VAS), and anxiety (as measured by the Corah Anxiety Scale). No statistically significant difference was found between the two groups for any patient demographic. All participants presented in moderate to severe pain, with initial pain ratings of 124 +/- 30 mm and 120 +/- 23 mm for the acetaminophen/ibuprofen/mock nasal spray group and placebo/intranasal ketorolac group, respectively.

Table 2 and Figure 1 show the average pain marked on a 170 mm VAS at each time interval (every 15 minutes for 240 minutes) for the acetaminophen/ibuprofen/mock nasal spray group and the placebo/intranasal ketorolac group. In each group, the efficacy of the drugs is demonstrated by participants reporting less perceived pain over time. A consistent decline in reported pain can be seen until approximately 120 minutes post-dosing, at which time reported pain remains relatively constant throughout the remainder of the study.

In addition to measuring reported pain, this study collected data on time to first sign of pain relief and time to meaningful pain relief (defined as the time when the

patients no longer focused on their pain) as seen in Table 3. Using the marked pain scores on the 170 mm VAS, time to 50% of the initial pain rating marked on the 170 mm VAS was calculated. Fifty percent pain relief was achieved at the 70 minute mark and 87 minute mark for the acetaminophen/ibuprofen/mock nasal spray group and placebo/intranasal ketorolac group, respectively. Table 3 reveals no statistically significant difference between either group for time to first sign of pain relief, time to meaningful pain relief, or time to 50% of initial pain.

Using the type 3 test of fixed effects, the data was statistically analyzed for group, time, or group/time interaction. As Table 4a shows, a statistically significant group/time interaction was observed. However, when the groups were compared at the same time interval, the differences were not statistically significant, as seen in Table 4b, indicating that there was no statistically significant difference in average pain between the acetaminophen/ibuprofen and intranasal ketorolac groups at each respective recorded time interval.

Chapter 4: Discussion

There were no statistically significant differences seen between the acetaminophen/ibuprofen/mock nasal spray group (n=34) and the placebo/intranasal ketorolac group (n=36) in regard to sex, age, weight, initial pain, or anxiety. As sex, age, and weight have been shown to affect the pharmacokinetics of drug metabolism and sex and age have been shown to influence pain perception, it is important to have groups that are similar for these indicators (24-27). Participants were representative of patients in need of adequate pain management prior to endodontic treatment, with both groups presenting with mean pain levels correlating to severe pain on a 170 mm VAS. Additionally, in single-dose acute pain studies, the inclusion of participants experiencing more intense pain allows for better discrimination of efficacy between active treatments (28). Participants in each group presented with similar anxiety scores, which is valuable as anxiety has also been shown to be strongly associated with pain experience (29).

With increasing numbers of deaths due to opioid-related overdose each year, the need for effective, non-opioid pain relievers is greater than ever (30). From 1999-2016, more than 350,000 people died from an overdose involving any opioid, including prescription and illicit opioids (30). Of the over 63,600 drug overdose deaths in 2016, 66% of those involved an opioid (30).

In dentistry, opioid containing medications have not been shown to be more effective at managing dental pain than NSAIDs (2). Conversely, NSAIDs have been

shown to have greater pain management efficacy for non-traumatic dental conditions (i.e. toothache), fewer adverse effects, and no abuse potential (31).

Studying pain preoperatively in an endodontic model is valuable for several reasons. First, this study design provides important information in regard to preoperative pain management, which is especially important in an endodontic model as treatment may not always be able to be rendered immediately or patients may not seek care immediately. Nusstein et al. showed that on average, patients with symptomatic irreversible teeth delayed care for 9 days and patients with symptomatic necrotic teeth delayed care for 4 days (32). Secondly, it allows the efficacy of the drugs to be studied without the confounding factor of treatment, since root canal treatment helps to alleviate patients' pain. In this way, we were able to observe the effect of the active drugs in a model where nothing has been done to alleviate the participants' discomfort other than administration of medication. As a result, this likely provides a more accurate representation of the medications' postoperative capabilities.

A few of the most significant predictors of postoperative pain in an endodontic model are the presence of preoperative pain and a preoperative diagnosis of symptomatic apical periodontitis (15). As a result, participants selected for our study presented with moderate to severe pain and a pulpal diagnosis of either symptomatic irreversible pulpitis or symptomatic pulpal necrosis, but all participants presented with symptomatic apical periodontitis.

There is a significant need for studies evaluating pain management in endodontic models as a recent systematic review concluded that there is currently insufficient

evidence to recommend the most effective NSAID, dose amount, or dose interval for endodontic patients experiencing postoperative pain (14-15, 21), and there are currently no systematic reviews exploring management of preoperative endodontic pain, as the endodontic literature on preoperative pain is sparse. Historically, the classic postoperative third-molar oral surgery extraction model has been used to extrapolate pain medication regimens to other branches of dentistry, including endodontics. However, patients presenting for third molar extraction are oftentimes asymptomatic, with no pain of inflammatory origin. This is distinctly different from an endodontic model, where pain preoperatively and postoperatively are of inflammatory origin. Since patients seeking endodontic care may have had pain of inflammatory origin for an extended period of time, the pain has potential to manifest peripherally and centrally (14, 33). As a result, employing pain management strategies that are designed to treat acute pain generated in previously non-inflamed tissues (i.e. third molar oral surgery extraction model) may not be applicable to an acute exacerbation of a chronically inflamed condition, as seen in endodontics (21).

In 2010, the non-steroidal antinflammatory drug ketorolac became available in intranasal form (Sprix®). Intranasal ketorolac offers the advantage of a pharmacokinetic profile almost identical to that of intramuscular ketorolac, a drug that has been proven to provide effective, non-opioid pain relief in patients requiring pain relief at the opioid level, in a form that a patient can self-administer at home (3-8). General advantages of an intranasal route of administration include: faster absorption time, lack of first-pass metabolism, faster time to pain relief, ease of use, patient tolerability, and ability of use

when patient is nauseated (8, 10). Ketorolac is the first, and likely only, NSAID available for effective intranasal administration due to its high water solubility (9). Due to its well-documented efficacy in pain management in all its available forms and the ability to now administer it at home, ketorolac in intranasal form was selected as an active medication for this study.

The comparative medication for this study was an acetaminophen/ibuprofen combination. It is thought by many to be the "gold standard" postoperative pain management recommendation given to patients experiencing dental pain. In two Cochrane Reviews, Derry et al. and Bailey et al. found a combination of ibuprofen/acetaminophen provided better pain relief than either drug alone for a longer period of time and with fewer side effects in an oral surgery model (11-12). There is pharmacologic evidence for this observation, as their effect is not additive, rather, the drugs work synergistically to provide superior pain relief (14).

Despite these reports, the acetaminophen/ibuprofen combination may not be the most popular drug recommendation among endodontists. Ibuprofen 600 mg alone has been found to be the most popular choice among endodontists, regardless of clinical scenario (34). This finding is likely multifactorial. Recommending a combined pain medication regimen may be more confusing for the patient to follow, and there is a greater opportunity for adverse reactions when two medications are administered versus one, simply due to the fact that the patient is exposing themselves to two different medications and therefore has potential to react adversely to one or both of them. Additionally, studies from Wells et al, Stamos et al, and Smith et al have shown no

difference in efficacy when prescribing an acetaminophen/ibuprofen combination versus ibuprofen alone in an endodontic postoperative pain model (14, 22, 35).

Since this study was designed as a single-dose acute pain study, the decision was made to use the combination of acetaminophen/ibuprofen instead of ibuprofen alone as the risk of adverse effects with a single dose combination administration are very low. Additionally, using a combination of two medications with different mechanisms of action that have proven to act synergistically when given together, as seen with acetaminophen/ibuprofen, makes this combination one of the more desirable over-the-counter combinations we can recommend (14). Therefore, using a combination of acetaminophen/ibuprofen as our comparative analgesic provides a high standard of pain relief for another medication (intranasal ketorolac) to be compared against.

Like ketorolac, ibuprofen is a NSAID and exerts its antinflammatory effect by inhibiting the production of prostaglandins by blocking the cyclooxygenase (COX) enzyme (24). In this study, a dose of 600 mg was chosen because at doses >600 mg, an increased fraction of unbound ibuprofen is observed, resulting in increased clearance and decreased area under the curve of the total drug (24). Therefore, there is little advantage to prescribing the maximum recommended dose of 800 mg over 600 mg. In addition, in the Modified Oxford League Table of Analgesic Efficacy, 600 mg of ibuprofen and 800 mg ibuprofen have the same number needed to treat (NNT) of 1.7, implying that little benefit is achieved with the higher dosage (26). NNT is the proportion of patients achieving at least 50% pain relief over 4-6 hours when compared with placebo in

randomized, double-blind, single-dose studies in patients experiencing moderate to severe pain.

Acetaminophen is a member of the aniline family of analgesics. For many years, the mechanism of action of acetaminophen was unknown. However, its mechanism of action has recently been elucidated. Acetaminophen exerts its effects at peripheral, spinal, and supraspinal locations (26). It decreases prostaglandin synthesis by inhibiting COX-1 and -2, scavenging peroxynitrite (an activator of COX), and inhibiting peripheral and central synthesis of prostaglandin E2. In addition, acetaminophen inhibits the opioid, cannabinoid, and serotonergic neurotransmitter systems. Lastly, its active metabolite, AM404, induces analgesia through a supraspinal mechanism by targeting TRPV1. Recently, acetaminophen has been found to be the leading cause of acute liver failure in the United States, resulting in a call for a decreased recommended max daily dose of 4 g administered as 1000 mg every 6 hours or 650 mg every 4 hours (26, 36). These risks are minimized further in this study as the drugs were administered as a single dose, and therefore reaching maximum dose was not a concern. As a result of these recommendations and 1000 mg acetaminophen having a NNT of 3.8 versus 600/650 mg acetaminophen having a NNT of 4.6, we chose to utilize a dose of 1000 mg of acetaminophen in this study (37).

Current literature comparing ketorolac in any route of administration to ibuprofen alone, acetaminophen alone, or an acetaminophen/ibuprofen combination are exceedingly sparse. A study by Forbes et al found oral ketorolac to have similar efficacy to ibuprofen alone, and greater efficacy than acetaminophen alone (38). An acetaminophen/ibuprofen

combination was not evaluated. A study by Naidu et al found oral ketorolac to have superior efficacy to a combination of acetaminophen/ibuprofen (38). However, ibuprofen alone or acetaminophen alone was not evaluated. Additionally, in both of these studies, the doses of ibuprofen and acetaminophen were much lower than the dose employed in this study. There are currently no studies comparing intranasal ketorolac to another non-opioid pain medication.

In our study, the time to peak reduction in pain as marked on a 170 mm VAS occurred around 120 minutes for the acetaminophen/ibuprofen/mock nasal spray group and the placebo/intranasal ketorolac group as seen in Figure 1 and Table 2, with no significant differences between the groups at any measured time interval. For the placebo/intranasal ketorolac group, this is consistent with results from previous studies (8, 40, 41), but significantly different than the findings from others, who found it to be much later (240-360 minutes) (3, 5, 10). These differences may be due to inadequate dose/time intervals in the Turner study, and differences between an endodontic model and a medical surgery model for the Singla and Moodie studies. Other studies did not record pain intensity frequently enough to discern if the results differed significantly from ours or not (6-7).

While the peak pain relief observed for acetaminophen/ibuprofen does not correlate with the reported peak plasma levels of acetaminophen (30-60 minutes), there is a correlation with the peak plasma concentration of ibuprofen (120 minutes). This may be a result of endodontic pain being primarily of inflammatory origin as ibuprofen targets inflammatory pain more effectively than acetaminophen due to its mechanism of action.

This is seen in a recent systematic review that found that the combination of 1000 mg acetaminophen/600 mg ibuprofen is more effective than placebo, but not significantly different from ibuprofen alone in endodontic models (14, 22, 35). Additionally, of the 15 studies included in this systematic review, only one of the 15 recorded pain data frequently enough to observe when peak pain relief occurred. In that study, peak pain relief from an acetaminophen/ibuprofen combination was seen at one hour as measured by pain intensity on a VAS, but peak pain relief as rated on a 1-4 categorical scale was seen at 3 hours (42).

On the recommendations of a meeting held by the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT) which focused on single-dose, short-duration trials, the additional pain efficacy indicators of “time to first sign pain relief,” “time to meaningful pain relief,” and “time to 50% of initial pain” were used to evaluate pain relief (28).

In this study, the average time to first sign of pain relief was found to be 39 minutes for the acetaminophen/ibuprofen/mock nasal spray group and 42 minutes for the placebo/intranasal ketorolac group as seen in Table 3, with no statistically significant differences between the groups. Considering the standard deviation in our results, our results are comparable to those found in a previous study evaluating time to first sign of pain relief for a combination of acetaminophen/ibuprofen (43) and a study evaluating time to first sign of pain relief for intranasal ketorolac (7). It is interesting to note that, in our study, the average time to first pain relief was found to be similar to reported peak plasma concentrations of intranasal ketorolac and acetaminophen. This observation is

reasonable, as the peak plasma concentration of acetaminophen is observed to be 30-60 minutes, whereas ibuprofen does not reach peak plasma concentration until 120 minutes (26, 44). Therefore, for the acetaminophen/ibuprofen group, the initial onset of pain relief may be brought on by the acetaminophen. The onset time of pain relief may also have been affected by the use of standard ibuprofen acid in this study as Khan et al have shown that ibuprofen formulated as ibuprofen sodium dihydrate has a faster onset of pain relief than regular ibuprofen acid (45). It is also interesting to note that in Figure 1, average pain scores are observed to have decreased from time zero to the first observation point (15 minutes), yet overall the participants did not indicate "first sign to pain relief" until approximately three observation periods past time zero. This indicates that the participants may not have understood the instructions they were given and/or may have lacked the ability to discern between "first sign to pain relief" and "meaningful pain relief." For example, only two participants did not stop the timer indicating "time to first sign of pain relief," yet their reported pain scores reached levels considered to be "mild pain" on the VAS during the study, further indicating that some participants may not have fully understood the instructions they were given.

In this study, the average time to meaningful pain relief was found to be 67 minutes for the acetaminophen/ibuprofen/mock nasal spray group and 79 minutes for the placebo/intranasal ketorolac group as seen in Table 3, with no statistically significant differences between the groups. Our data indicates that meaningful pain relief was achieved approximately 30 minutes after participants reported first sign of pain relief. While few studies exist evaluating this point for these drugs, our results are similar to

previous studies evaluating the average time to meaningful pain relief for intranasal ketorolac (6-7), but significantly different from a study evaluating the average time to meaningful pain relief for a combination of acetaminophen/ibuprofen (43). The more rapid pain relief observed in our study may be due to the patient population being untreated, the difference in pain in an oral surgery model versus pain in an endodontic model, or some combination of the two.

It is worth noting that 12 participants did not stop the timer indicating "time to meaningful pain relief." However, 5 of those 12 reported pain scores on the VAS correlating to "mild pain" at some point during the duration of the study, implying that patients may not have understood the directions they were given for this indicator or that some patients may be expecting to receive complete pain relief from the medications. The remaining 7 patients (4 (12%) from the acetaminophen/ibuprofen group and 3 (8%) from the intranasal ketorolac group) did not report a pain score below moderate or severe pain on the VAS during their participation in the study.

In this study, the average time to 50% of initial pain was calculated to be 70 minutes for the acetaminophen/ibuprofen/mock nasal spray group and 87 minutes for the placebo/intranasal ketorolac group, with no statistically significant difference between the groups. While few studies exist evaluating this point for these drugs, our results are similar to a previous study evaluating the time to 50% of initial pain relief for a combination of acetaminophen/ibuprofen (43). No studies available currently have calculated the average time to 50% of initial pain using intranasal ketorolac. It is interesting to note that there is very little difference (+3 minutes for the

acetaminophen/ibuprofen/mock nasal spray group and +8 minutes for the placebo/intranasal ketorolac group) in the self-reported "time to meaningful pain relief" and the investigator-calculated "time to 50% of initial pain." This observation suggests that 1) time to 50% of initial pain can be used as an effective, objective measurement of clinically meaningful pain relief and 2) pain does not need to be completely resolved for patients to feel they have achieved meaningful relief.

There were 13 patients (19%) that did not report pain scores representing 50% of their initial reported pain at any time point during the study, 6 (18%) from the acetaminophen/ibuprofen group and 7 (19%) from the intranasal ketorolac group. However, of the 13 patients for whom 50% of pain relief was not achieved, only 5 participants (3 in the acetaminophen/ibuprofen group and 2 in the intranasal ketorolac group) did not indicate that they received "meaningful" pain relief. This reiterates the observation above that pain does not need to be completely resolved for most patients to feel they have achieved meaningful relief.

Upon examination of individual reported pain scores, it was found that 4 participants in each group (11% in intranasal ketorolac and 12% in acetaminophen/ibuprofen group) received little to no pain relief during their participation in the study. It is worth noting, however, that only one of those participants (from the acetaminophen/ibuprofen group) requested to be removed from the study due to lack of pain relief.

Information on adverse effects was collected in this study by asking the participants to report any "effects" felt during administration of the medication and

throughout the duration of the study (see Appendix H). The wording of the questions were intended to elicit effects responses from participants and were carefully chosen to avoid leading the participant and to avoid investigator bias (28). As in previous studies, the most common side effects reported with intranasal ketorolac were related to its route of administration and included nasal burning (78%), increased lacrimation (27%), and rhinorrhea (25%) (46). The effects were mild and transient, with only one patient (2%) stating that she would only choose the nasal spray for pain relief if there was no other option. While significantly fewer side effects were associated with the acetaminophen/ibuprofen/mock nasal spray group (most common: bad taste (11%), headache (8%), and drowsiness (8%)), this is likely due to the triad of nasal burning, increased lacrimation, and rhinorrhea often being reported together in the intranasal ketorolac group. While this makes it appear that intranasal ketorolac had a significantly greater number of side effect events (69 events in intranasal ketorolac group versus 18 in the acetaminophen/ibuprofen group), the triad of side effects mentioned above artificially inflated that number.

During this study, no participants requested to be removed from the study due to side effects and only one participant requested to be removed from the study due to inadequate pain relief. There were participants, however, who did not participate for the entire 240 minute duration of the study. The majority of these participants stated at the beginning of the study that they were unable to stay for the entire 240 minutes and therefore, a set time period that they would participate was established at the beginning of the study. Some participants agreed to participate in the study until they could be seen for

treatment. Others had to depart the study early due to unforeseen family issues that required them to leave the clinic. Unlike many medical study models, patients were not required to remain under clinical observation for a set period of time after a procedure. Additionally, some participation times were limited by clinic hours. For example, if a participants agreed to enroll in the study at 2:00 PM, three hours of data would be collected as the clinic closes at 5:00 PM. All participants, however, recorded at least 120 minutes of data. Sixty participants recorded 180 minutes of data, and 52 participants completed the full 240 minutes. It is important to emphasize that these numbers do not represent a "dropout rate" as observed in many pain studies, and therefore it cannot be concluded that participants left the study due to inadequate pain relief or deleterious side effects. This study only had one participant "drop out" due to inadequate pain management.

In summary, this study found that the effectiveness of intranasal ketorolac was not significantly different from that of a 1000 mg acetaminophen/600 mg ibuprofen combination. The efficacy of the acetaminophen/ibuprofen combination has been well established in oral surgery models, and this study demonstrated its efficacy in an endodontic model. However, studies that report no significant difference between a combination of acetaminophen/ibuprofen and ibuprofen alone in endodontic models, begs the question if the combination is actually superior or if the ibuprofen present in the combination is responsible for the participants' pain relief (14, 22, 35). Since no ibuprofen only group was included here, this is clearly an important area for future research.

Currently, intranasal ketorolac is relatively expensive (approximately $1000 for a 5 day supply). Like many medications, drugs are more expensive when they are first introduced to the market. However, good insurance coverage can make these drugs much more affordable. Additionally, the patents that apply to Sprix® are set to expire in December 2018, at which point intranasal ketorolac will be able to be produced in generic form (47). Amneal Pharmaceuticals has expressed interest in producing the generic form of this drug; in fact, they initiated production in 2012 and were concomitantly sued by the owner of Sprix® to cease production until the patents expire late in 2018 (47). Therefore, the competitive market will likely drive a decrease in price of the brand name (Sprix®) and the generic form, as it becomes available.

In conclusion, intranasal ketorolac's performance in this study reveals that it provides rapidly acting, effective pain relief for endodontic patients experiencing moderate to severe pain of endodontic origin. Since 1989, IM and IV ketorolac have been extensively researched and utilized in medical models as a non-opioid pain medication for patients requiring pain management at the opioid level. Oral ketorolac is only FDA approved for use after IM or IV administration of ketorolac. Therefore, ketorolac's availability for use in intranasal form without the requirement of previous IM or IV administration has important implications for preoperative at-home use and postoperative outpatient settings (i.e. endodontics).

Intranasal ketorolac provides a non-narcotic alternative and an additional route of medication administration to the practicing clinician. Effective pain management alternatives like intranasal ketorolac are immensely valuable as we know not all patients

receive equal pain relief from medications (48). A Cochrane review of single dose oral analgesics shows this to be true by finding that only 70% of patients achieved good pain relief with the "best" drug reviewed, and 30% with the worst (48). There is no one drug that is best for everyone. Having both of these drugs in a clinician's arsenal means if a patient is not responding well to an acetaminophen/ibuprofen combination, that clinician may have potential for pain relief for that patient by prescribing intranasal ketorolac and vice versa. Additionally, the value of an intranasal route cannot be overstated, as it avoids the first-pass metabolism, allows for rapid onset even if the patient has recently eaten, and is a viable option when patients are nauseous.

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Chapter 5: Summary and Conclusions

In conclusion, intranasal ketorolac provides an interesting alternative for clinicians in managing preoperative and postoperative endodontic pain and provides an additional route of administration. It provides rapid and effective pain relief comparable to the commonly used acetaminophen/ibuprofen combination regimen. With the worsening of the opioid crisis and the numerous side effects associated with opioids, having multiple effective, non-opioid options available in varying forms of administration is invaluable to practicing clinicians.

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Appendix A
Tables

Table 1 Demographics of Patient Groups

	Acetaminophen/Ibuprofen (n=34)	**Intranasal Ketorolac (n=36)**	**P-Value**
Sex	15/34 (44%) Male 19/34 (56%) Female	19/36 (53%) Male 17/36 (47%) Female	0.4687*
Mean Age (yrs)	33 +/- 11	33+/- 9	0.9247**
Mean Weight (lbs)	179 +/- 47	189 +/- 52	0.3677**
Mean Initial Pain (mm)	124 +/- 30	120 +/- 23	0.5988**
Corah Anxiety Score (median)	10 (5-20)	10 (4-18)	0.7102***

*Chi Squared

** Randomization Test

***Wilcoxon Rank Sum Test

Table 2 Average Pain Marked on 170 mm VAS at Each Time Period

Time (mins)	Acetaminophen/Ibuprofen (mm)	Intranasal Ketorolac (mm)	P-value
0	122 +/- 32	114 +/- 28	1.000
15	112 +/- 34	109 +/- 26	1.000
30	91 +/- 39	99 +/- 34	1.000
45	76 +/- 40	85 +/- 39	1.000
60	64 +/- 42	74 +/- 41	1.000
75	54 +/- 42	69 +/- 38	0.9996
90	48 +/- 40	60 +/- 38	1.000
105	46 +/- 41	52 +/- 37	1.000
120	45 +/- 44	48 +/- 38	1.000
135	42 +/- 43	51 +/- 42	1.000
150	36 +/- 38	46 +/- 42	1.000
165	36 +/- 38	43 +/- 38	1.000
180	36 +/- 37	44 +/- 37	1.000
195	41 +/- 41	40 +/- 34	1.000
210	40 +/- 41	36 +/- 35	1.000
225	43 +/- 41	36 +/- 36	1.000
240	46 +/- 46	36 +/- 38	1.000

Table 3 Time to Pain Relief

	Acetaminophen/Ibuprofen	Intranasal Ketorolac	P-value*
Time to First Sign of Pain Relief (min)	39 +/- 32	42 +/- 29	0.6846
Time to Meaningful Pain Relief (min)	67 +/- 44	79 +/- 39	0.2603
Time to 50% of Initial Pain (min)	70 +/- 35	87 +/- 50	0.1311

*Type 3 Test of Fixed Effects

Table 4 Test of Fixed Effects and Difference of Least Squares Means

a. Type 3 Test of Fixed Effects

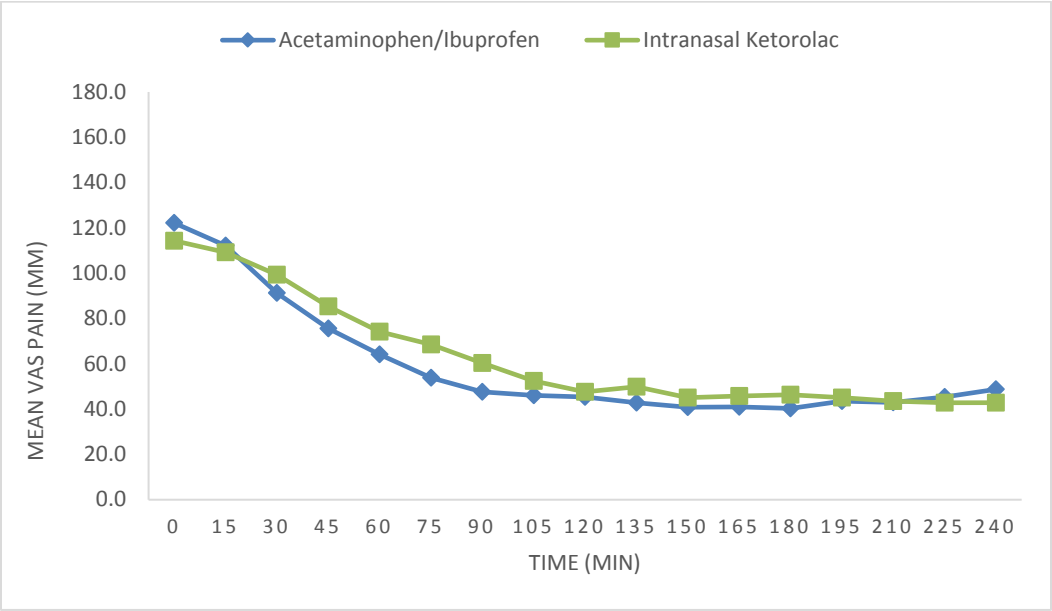
	P-value
GROUP	0.5982
TIME	<.0001
GROUP*TIME	0.0219

b. Differences of Least Squares Means for Acetaminophen/Ibuprofen versus Intranasal Ketorolac

	Control Group	Treatment Group	Time (min)	Estimate	Standard Error	Adjusted P- value
GROUP*TIME	Acetaminophen/Ibuprofen	Intranasal Ketorolac	0	7.8431	8.9817	1.0000
GROUP*TIME	Acetaminophen/Ibuprofen	Intranasal Ketorolac	15	3.0114	8.9817	1.0000
GROUP*TIME	Acetaminophen/Ibuprofen	Intranasal Ketorolac	30	-8.0703	8.9817	1.0000
GROUP*TIME	Acetaminophen/Ibuprofen	Intranasal Ketorolac	45	-9.7745	8.9817	1.0000
GROUP*TIME	Acetaminophen/Ibuprofen	Intranasal Ketorolac	60	-9.9886	8.9817	1.0000
GROUP*TIME	Acetaminophen/Ibuprofen	Intranasal Ketorolac	75	-14.7598	8.9817	0.9996
GROUP*TIME	Acetaminophen/Ibuprofen	Intranasal Ketorolac	90	-12.7435	8.9817	1.0000
GROUP*TIME	Acetaminophen/Ibuprofen	Intranasal Ketorolac	105	-6.3317	8.9817	1.0000
GROUP*TIME	Acetaminophen/Ibuprofen	Intranasal Ketorolac	120	-2.3137	8.9817	1.0000
GROUP*TIME	Acetaminophen/Ibuprofen	Intranasal Ketorolac	135	-7.1538	9.026	1.0000
GROUP*TIME	Acetaminophen/Ibuprofen	Intranasal Ketorolac	150	-4.2264	9.0949	1.0000
GROUP*TIME	Acetaminophen/Ibuprofen	Intranasal Ketorolac	165	-4.8608	9.172	1.0000
GROUP*TIME	Acetaminophen/Ibuprofen	Intranasal Ketorolac	180	-6.0879	9.2393	1.0000
GROUP*TIME	Acetaminophen/Ibuprofen	Intranasal Ketorolac	195	-1.5398	9.3775	1.0000
GROUP*TIME	Acetaminophen/Ibuprofen	Intranasal Ketorolac	210	-0.5603	9.5092	1.0000
GROUP*TIME	Acetaminophen/Ibuprofen	Intranasal Ketorolac	225	2.5428	9.6236	1.0000
GROUP*TIME	Acetaminophen/Ibuprofen	Intranasal Ketorolac	240	5.959	9.7231	1.0000

Appendix B
Figures

Figure 1: Pain by Group and Time Period



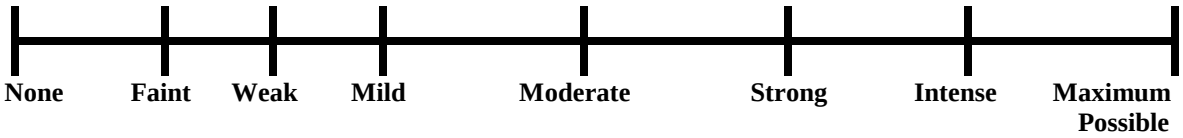
Appendix C
Initial Pain VAS

Initial Pain Rating*

Date: _____
Code #: _____

* NOTE: VAS not to scale.

1. Please mark a vertical line " | " on the line below to rank the level of pain you are feeling today.



Appendix D
Health History

The Ohio State University
College of Dentistry
FORM 1/97

Date _____
Date of Birth _____

Biographical Data _____

Chief Complaint (Why is the patient seeking dental care?) _____

_____

Present Illness (History of Chief Complaint) _____

MEDICAL HISTORY

1. Do you have or have you had any of the following?

a. rheumatic fever or rheumatic heart disease	NO	YES
b. heart murmur or mitral valve prolapse	NO	YES
c. heart disease/heart attack	NO	YES
d. artifical heart valve	NO	YES
e. irregular heart beat	NO	YES
f. pacemaker	NO	YES
g. high blood pressure	NO	YES
h. chest pains or angina	NO	YES
i. stroke	NO	YES
j. artificial joint	NO	YES
k. hepatitis/liver disease	NO	YES
l. tuberculosis (TB)	NO	YES
m. thyroid trouble	NO	YES
n. kidney disease	NO	YES
o. diabetes (sugar)	NO	YES
p. asthma	NO	YES
q. HIV or other immunosuppressive disease	NO	YES
r. radiation or cancer therapy	NO	YES

2. Do you have or have you had any disease, condition, or problem not listed here? NO YES

3. Have you ever been hospitalized? NO YES

4. Have you had excessive or prolonged bleeding requiring special treatment? NO YES

5. Have you had an allergic reaction to any drugs or medications?
(Circle all that apply: penicillin; codeine; aspirin; anesthetics; other) NO YES

6. Are you currently under the care of a physician (M.D., D.O.)? NO YES
When were you last seen by a physician? _____
Name of Physician _____
Street address _____
City, State, and Zip Code _____
Phone _____

7. Are you pregnant or nursing? Estimated Date of Delivery_____ NO YES

8. Have you had any trouble assosciated with previous dental treatment? NO YES

9. Do you have any lumps or sores in your mouth now? NO YES

10. Do you smoke or use smokeless tobacco? NO YES

11. How often do you have dental check ups? _____ Date of last Exam _____

12. Are you currently taking any drugs or medications (such as antibiotics, heart medicine, birth control pills?)..... NO YES

CURRENT MEDICATIONS

Trade Name	Generic Name	Dose/Frequency	Reason

I have reviewed the information I have provided, and to the best of my knowledge it is correct and complete.

SUMMARY OF PATIENT'S MEDICAL STATUS:_____

_____

_____

MEDICAL RISK ASSESSMENT (check one)

☐ ASA I (healthy individual)
☐ ASA II (mild systemic disease)
☐ ASA III (severe disease but not incapacitating)
☐ ASA IV (incapacitating systemic disease, constant threat to life)

MEDICAL CONSULATION REQUIRED

☐ No (healthy and/or stabilized disease)

☐ Yes (ASA III or IV; cardiac murmur; vague hx; recent major disease; recent diagnosis/operation; uncontrolled disease; blood pressure; etc.)

Does the chief complaint require emergency treatment?..... NO YES

_____ Student / I.D.# _____ Instructor / I.D.# _____ / / Date

Appendix E
Consent Form

The Ohio State University Consent to Participate in Research

Study Title: Pain Reduction in symptomatic irreversible pulpitis and symptomatic pulpal necrosis using ibuprofen/acetaminophen versus intranasal ketorolac (Sprix). FOR PARTICIPANTS WITH SYMPTOMATIC IRREVERSIBLE PULPITIS.

Principal Investigator: Dr. Melissa Drum

Sponsor: OSU Graduate Endodontics

- **This is a consent form for research participation.** It contains important information about this study and what to expect if you decide to participate. Please consider the information carefully. Feel free to discuss the study with your friends and family and to ask questions before making your decision whether or not to participate.
- **Your participation is voluntary.** You may refuse to participate in this study. If you decide to take part in the study, you may leave the study at any time. No matter what decision you make, there will be no penalty to you and you will not lose any of your usual benefits. Your decision will not affect your future relationship with The Ohio State University. If you are a student or employee at Ohio State, your decision will not affect your grades or employment status.
- **You may or may not benefit as a result of participating in this study.** Also, as explained below, your participation may result in unintended or harmful effects for you that may be minor or may be serious depending on the nature of the research.
- **You will be provided with any new information that develops during the study that may affect your decision whether or not to continue to participate.** If you decide to participate, you will be asked to sign this form and will receive a copy of the form. You are being asked to consider participating in this study for the reasons explained below.

1. Why is this study being done?

The purpose of this study is to evaluate the effect of ketorolac "Sprix" (drug nose spray) vs. acetaminophen/ibuprofen (Tylenol/Advil) on pain control in patients with painful live teeth.

2. How many people will take part in this study?

One Hundred people (100) will take part in this study.

3. What will happen if I take part in this study?

You have a tooth, which is hurting (painful), and you have elected to have a root canal or extraction. If you decide to participate in this study, you will be required to complete a medical history questionnaire, a HIPAA authorization and consent form. If you are a woman able to have children, you will be required to take a urine pregnancy test before participation. If you are a female and are pregnant or nursing, you will not be able to participate.

The tooth causing you pain will first be tested to make an accurate diagnosis. It will first be tested with a cold cotton pellet chilled with an ice spray. The cold test is used routinely before root canal treatment.

You will be asked to rate the pain you are having prior to any treatment. You will also fill out a form to rate how anxious you are. You will then randomly receive either intranasal ketorolac (pain drug) and a placebo (sugar pill) or intranasal placebo (saline) and ibuprofen/acetaminophen (pain drug). Neither your doctor nor you will know which one you will receive. Ketorolac is a non-steroidal anti-inflammatory (like Advil or Motrin) and is indicated for use of moderate to severe pain. Following taking of the drug, you will be released to the Graduate Endodontic waiting room and you will be asked to fill out a pain scale every 15 minutes for a total of 240 minutes (4 hours). You will also be asked to record with a stopwatch when you first feel any pain relief, and when the pain relief becomes meaningful to you. You will also be asked to record when you feel the pain relief is greater than 50% and whether or not you feel any adverse effects from the medications.

Should you experience significant pain, not relieved by the pain medication, or your pain returns to where you started before then end of the 240 minute period, anesthesia may be provided. The emergency root canal treatment will be set at a time as determined by you and your provider.

Your participation or non-participation will have no effect on whether you will receive emergency root canal treatment. You understand that if you want to save the painful tooth (provided it is restorable or savable) further root canal treatment and restorative treatment such as a filling and or a crown will be needed. You are responsible for the emergency root canal fee.

4. How long will I be in the study?

Your participation in the study will last approximately 4 hours, with an additional 15 minutes of paperwork at the beginning, during which time you will record information on your pain relief in the graduate endodontic waiting room. You may have the emergency endodontic procedure completed without participating in the study. You may choose not to participate without penalty or loss of benefits to which you are otherwise entitled.

5. Can I stop being in the study?

You may leave the study at any time. If you decide to stop participating in the study, there will be no penalty to you, and you will not lose any benefits to which you are otherwise entitled. Your decision will not affect your future relationship with The Ohio State University.

6. What risks, side effects or discomforts can I expect from being in the study?

Intranasal ketorolac (nose drug) may cause some nasal discomfort and irritation. The irritation is generally mild and transient, lasting less than 5 minutes. You may have an allergic reaction (rash, difficulty breathing) to ibuprofen, which is very rare, upset stomach, nausea, heartburn, or diarrhea which is very rare with one dose. You may have an allergic reaction (rash, difficulty breathing) to acetaminophen, which is very rare, upset stomach, or nausea which is also very rare with one dose.

If you are a woman able to have children, you will be questioned regarding pregnancy or suspected pregnancy and will not be allowed to participate if pregnant, suspect a pregnancy, trying to become pregnant, or nursing. Additionally, you will be required to take a urine pregnancy test before you can start this study. The reason for excluding pregnant or potentially pregnant women is an attempt to minimize this population in the study because the potential risks to the fetus and nursing baby are unknown.

Typically emergency endodontic treatment and/or extraction may be rendered on the day of diagnosis or at a time in the future as determined by the clinician's and your schedule.

7. What benefits can I expect from being in the study?

You will not directly benefit from this study other than possible pain reduction.

8. What other choices do I have if I do not take part in the study?

You may have the emergency endodontic procedure completed without participating in the study. You may choose not to participate without penalty or loss of benefits to which you are otherwise entitled.

9. Will my study-related information be kept confidential?

Efforts will be made to keep your study-related information confidential. However, there may be circumstances where this information must be released. For example, personal information regarding your participation in this study may be disclosed if required by state law.

Also, your records may be reviewed by the following groups (as applicable to the research):

- Office for Human Research Protections or other federal, state, or international regulatory agencies;
- U.S. Food and Drug Administration;
- The Ohio State University Institutional Review Board or Office of Responsible Research Practices;
- The sponsor supporting the study, their agents or study monitors; and
- Your insurance company (if charges are billed to insurance).

If this study is related to your medical care, your study-related information may be placed in your permanent hospital, clinic, or physician's office records. Authorized Ohio State University staff not involved in the study may be aware that you are participating in a research study and have access to your information.

A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. law. This website will not include information that can identify you. At most, the website will include a summary of the results. You can search the website at any time.

You may also be asked to sign a separate Health Insurance Portability and Accountability Act (HIPAA) research authorization form if the study involves the use of your protected health information.

10. What are the costs of taking part in this study?

The cost of the study drugs (acetaminophen/ibuprofen and intranasal ketorolac) will be covered. Other costs (parking, cost of endodontic treatment or extraction) will not be reimbursed in this study. The study will pay for the cost of the urine pregnancy test when indicated.

11. Will I be paid for taking part in this study?

Yes, you will receive up to a total of $80 in cash for participation in the study. $20 will be paid for enrolling in the study regardless of whether or not the study is completed. An additional $20 will be paid for each data collection period. Period 1 will be completed after 60 minutes, period 2 after 120 minutes, period 3 after 180 minutes and period 4 after 240 minutes. By law, payments to subjects are considered taxable income.

12. What happens if I am injured because I took part in this study?

If you suffer an injury from participating in this study, you should notify the researcher or study doctor immediately, who will determine if you should obtain medical treatment at The Ohio State University Wexner Medical Center.

The cost for this treatment will be billed to you or your medical or hospital insurance. The Ohio State University has no funds set aside for the payment of health care expenses for this study.

13. What are my rights if I take part in this study?

If you choose to participate in the study, you may discontinue participation at any time without penalty or loss of benefits. By signing this form, you do not give up any personal legal rights you may have as a participant in this study.

You will be provided with any new information that develops during the course of the research that may affect your decision whether or not to continue participation in the study.

You may refuse to participate in this study without penalty or loss of benefits to which you are otherwise entitled.

An Institutional Review Board responsible for human subjects research at The Ohio State University reviewed this research project and found it to be acceptable, according to applicable state and federal regulations and University policies designed to protect the rights and welfare of participants in research.

14. Who can answer my questions about the study?

For questions, concerns, or complaints about the study you may contact Dr. Melissa Drum or Dr. Kathryn Watts at 614-292-3596.

For questions about your rights as a participant in this study or to discuss other study-related concerns or complaints with someone who is not part of the research team, you may contact Ms. Sandra Meadows in the Office of Responsible Research Practices at 1-800-678-6251.

If you are injured as a result of participating in this study or for questions about a study-related injury, you may contact Dr. Melissa Drum or Dr. Kathryn Watts at 614-292-3596.

Signing the consent form

I have read (or someone has read to me) this form and I am aware that I am being asked to participate in a research study. I have had the opportunity to ask questions and have had them answered to my satisfaction. I voluntarily agree to participate in this study.

I am not giving up any legal rights by signing this form. I will be given a copy of this form**.**

Printed name of subject	**Signature of subject**
	AM/PM
	Date and time
Printed name of person authorized to consent for subject (when applicable)	**Signature of person authorized to consent for subject (when applicable)**
	AM/PM
Relationship to the subject	**Date and time**

Investigator/Research Staff

I have explained the research to the participant or his/her representative before requesting the signature(s) above. There are no blanks in this document. A copy of this form has been given to the participant or his/her representative.

Printed name of person obtaining consent	**Signature of person obtaining consent**
	AM/PM
	Date and time

Witness(es) - *May be left blank if not required by the IRB*

Printed name of witness	**Signature of witness**
	AM/PM
	Date and time
Printed name of witness	**Signature of witness**
	AM/PM
	Date and time

Appendix F
Privacy Form

THE OHIO STATE UNIVERSITY
AUTHORIZATION TO USE
PERSONAL HEALTH INFORMATION IN RESEARCH

Title of the Study: Pain reduction in symptomatic irreversible pulpitis using ibuprofen/acetaminophen versus intranasal ketorolac (Sprix)

Protocol Number: 2016H0436

Principal Investigator: Dr. Melissa Drum

Subject Name_____

Before researchers use or share any health information about you as part of this study, The Ohio State University is required to obtain your authorization. This helps explain to you how this information will be used or shared with others involved in the study.

- The Ohio State University and its hospitals, clinics, health-care providers, and researchers are required to protect the privacy of your health information.
- You should have received a Notice of Privacy Practices when you received health care services here. If not, let us know and a copy will be given to you. Please carefully review this information. Ask if you have any questions or do not understand any parts of this notice.
- If you agree to take part in this study your health information will be used and shared with others involved in this study. Also, any new health information about you that comes from tests or other parts of this study will be shared with those involved in this study.
- Health information about you that will be used or shared with others involved in this study may include your research record and any health care records at The Ohio State University. For example, this may include your medical records, x-rays, or laboratory results. Psychotherapy notes in your health records (if any) will not, however, be shared or used. Use of these notes requires a separate, signed authorization.

Please read the information carefully before signing this form. Please ask if you have any questions about this authorization, the university's Notice of Privacy Practices or the study before signing this form.

Those Who May Use, Share, and Receive Your Information as Part of This Study

- Researchers and staff at The Ohio State University will use, share, and receive your personal health information for this research study. Authorized Ohio State staff not involved in the study may be aware that you are participating in a research study and have access to your information. If this study is related to your medical care, your study-related information may be placed in your permanent hospital, clinic, or physician's office records.

Initials/Date: _____

Those who oversee the study will have access to your information, including the following:

  - Members and staff of The Ohio State University's Institutional Review Boards, including the Western Institutional Review Board
  - The Ohio State University Office of Responsible Research Practices
  - University data safety monitoring committees
  - The Ohio State University Office of Research.

- Your health information may also be shared with federal and state agencies that have oversight of the study or to whom access is required under the law. These may include the following:
  - Food and Drug Administration
  - Office for Human Research Protections
  - National Institutes of Health
  - Ohio Department of Job and Family Services.

- These researchers, companies and/or organization(s) outside of The Ohio State University may also use, share and receive your health information in connection with this study:
  - None

The information that is shared with those listed above may no longer be protected by federal privacy rules.

Authorization Period

This authorization will not expire unless you change your mind and revoke it in writing. There is no set date at which your information will be destroyed or no longer used. This is because the information used and created during the study may be analyzed for many years, and it is not possible to know when this will be completed.

Initials/Date_____

Signing the Authorization

- You have the right to refuse to sign this authorization. Your health care outside of the study, payment for your health care, and your health care benefits will not be affected if you choose not to sign this form.
- You will not be able to take part in this study and will not receive any study treatments if you do not sign this form.

- If you sign this authorization, you may change your mind at any time. Researchers may continue to use information collected up until the time that you formally changed your mind. If you change your mind, your authorization must be revoked in writing. To revoke your authorization, please write to: *Dr. Melissa Drum at the College of Dentistry, 305 w 12th avenue, the Ohio State University, Columbus, Ohio 43218 or Dr. Henry Fischbach at the College of Dentistry, 305 w 12th avenue, the Ohio State University, Columbus, Ohio 43218.*
- Signing this authorization also means that you will not be able to see or copy your study-related information until the study is completed. This includes any portion of your medical records that describes study treatment.

Contacts for Questions

- If you have any questions relating to your privacy rights, please contact: *Dr. Henry Fischbach at the College of Dentistry, 305 w 12th avenue, the Ohio State University, Columbus, Ohio 43218. Phone:(614)292-6983.*
- If you have any questions relating to the research, please contact: *Dr. Melissa Drum at the College of Dentistry, 305 W. 12th Ave., The Ohio State University, Columbus, OH 43210. Phone:(614)292-3596.*

Signature

I have read (or someone has read to me) this form and have been able to ask questions. All of my questions about this form have been answered to my satisfaction. By signing below, I permit *Dr. Melissa Drum* and the others listed on this form to use and share my personal health information for this study. I will be given a copy of this signed form.

Signature_____
(Subject or Legally Authorized Representative)

Print Name _____ Date_____ Time _____
AM/PM

_____
(If legal representative, also print relationship to subject)

Appendix G
Pain Intensity Scores, 15 Minute Intervals

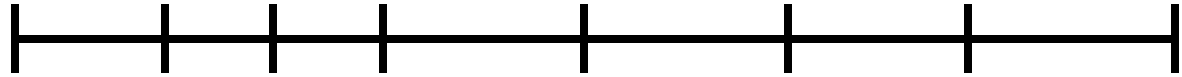
Pain Intensity Scores, 15 Minute Intervals*

Date: _____ Time Drug Administered: _____

Code #: _____

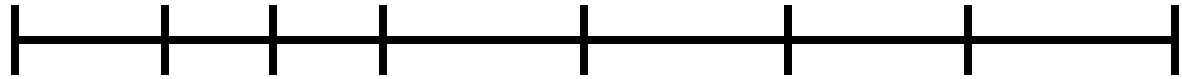
*NOTE: VAS not to scale.

240 minutes. Please mark a vertical line "|" on the line below to rank the level of pain you are feeling.



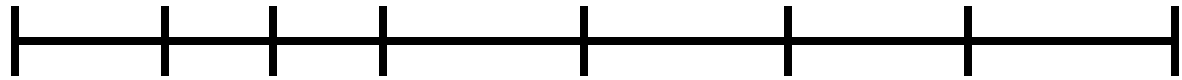
None **Faint** **Weak** **Mild** **Moderate** **Strong** **Intense** **Maximum Possible**

225 minutes. Please mark a vertical line "|" on the line below to rank the level of pain you are feeling.



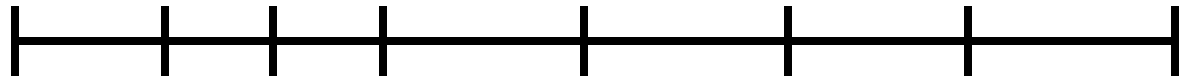
None **Faint** **Weak** **Mild** **Moderate** **Strong** **Intense** **Maximum Possible**

210 minutes. Please mark a vertical line "|" on the line below to rank the level of pain you are feeling.



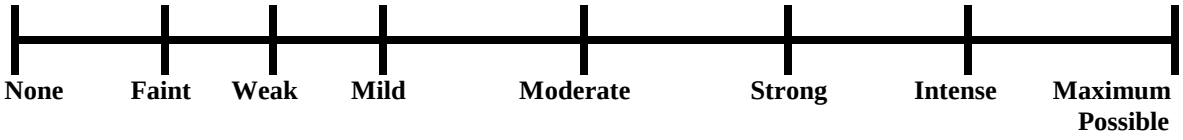
None **Faint** **Weak** **Mild** **Moderate** **Strong** **Intense** **Maximum Possible**

195 minutes. Please mark a vertical line "|" on the line below to rank the level of pain you are feeling.

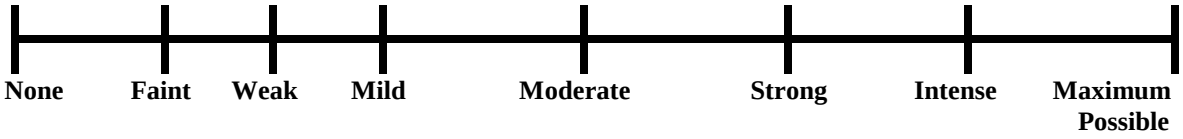


None **Faint** **Weak** **Mild** **Moderate** **Strong** **Intense** **Maximum Possible**

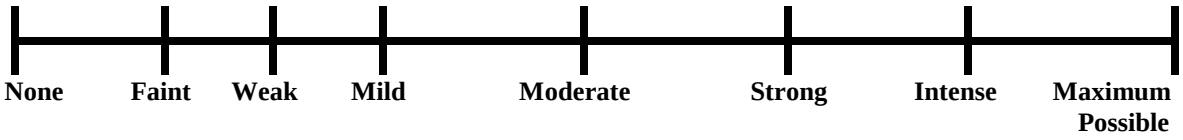
180 minutes. Please mark a vertical line "|" on the line below to rank the level of pain you are feeling.



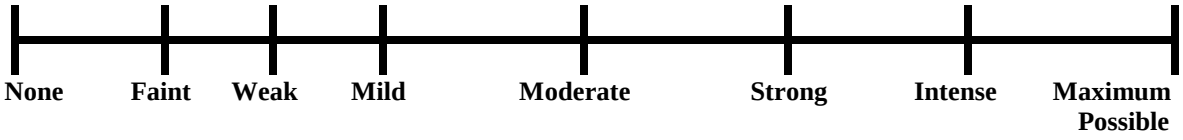
165 minutes. Please mark a vertical line "|" on the line below to rank the level of pain you are feeling.



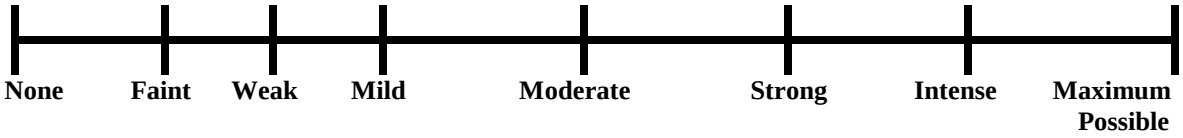
150 minutes. Please mark a vertical line "|" on the line below to rank the level of pain you are feeling.



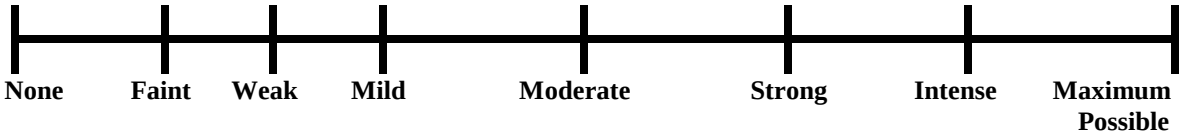
135 minutes. Please mark a vertical line "|" on the line below to rank the level of pain you are feeling.



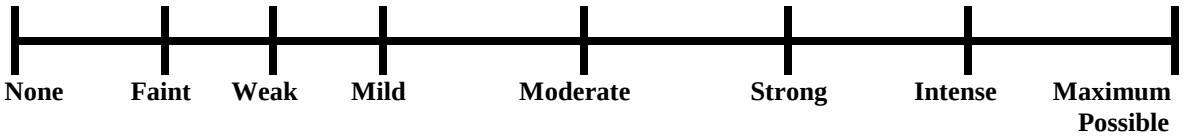
120 minutes. Please mark a vertical line "|" on the line below to rank the level of pain you are feeling.



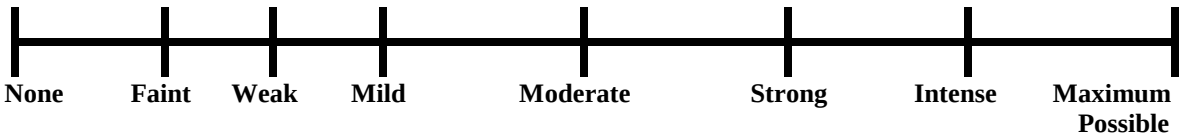
105 minutes. Please mark a vertical line "|" on the line below to rank the level of pain you are feeling.



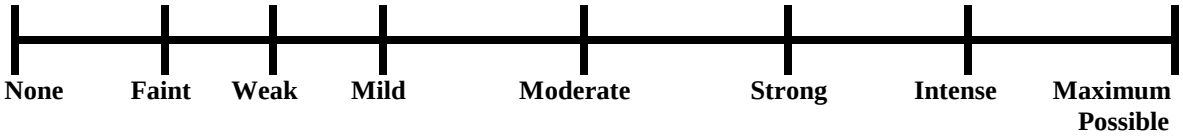
90 minutes. Please mark a vertical line "|" on the line below to rank the level of pain you are feeling.



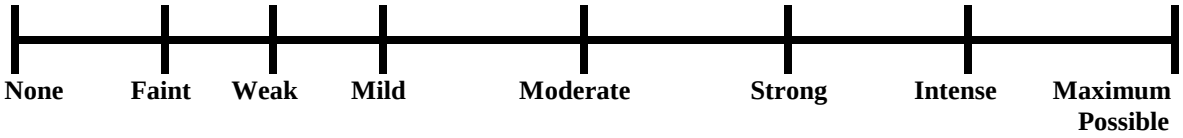
75 minutes. Please mark a vertical line "|" on the line below to rank the level of pain you are feeling.



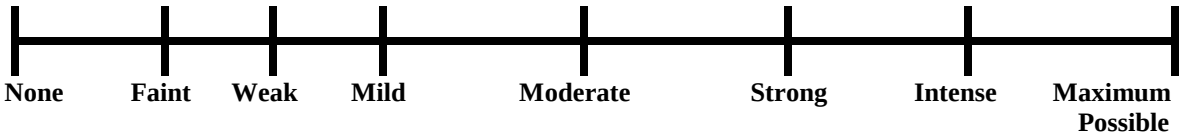
60 minutes. Please mark a vertical line "|" on the line below to rank the level of pain you are feeling.



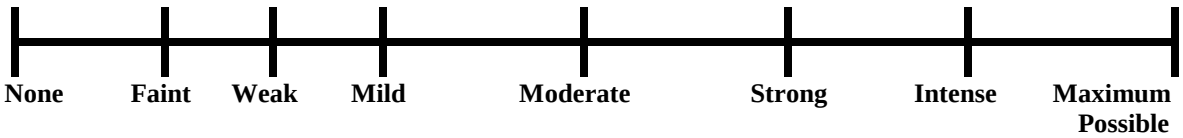
45 minutes. Please mark a vertical line "|" on the line below to rank the level of pain you are feeling.



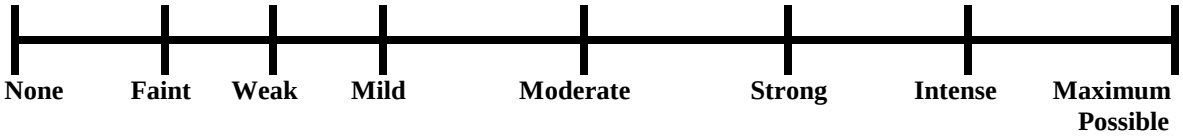
30 minutes. Please mark a vertical line "|" on the line below to rank the level of pain you are feeling.



15 minutes. Please mark a vertical line "|" on the line below to rank the level of pain you are feeling.



0 minutes. Please mark a vertical line "|" on the line below to rank the level of pain you are feeling.



Appendix H
Additional Pain Information

Comments after Medication Administration

Please note any effects experienced during medication administration below.

_____
_____
_____
_____
_____
_____
_____

Additional Pain Information

_____ Record the stopwatch time when you **first feel pain relief**.

_____ Record the stopwatch time when your **pain relief becomes meaningful to you** (when you no longer focus on the pain).

Effects from Medications/Comments

If you feel any effects from the medications during the study, please record them below.

_____
_____
_____
_____
_____
_____
_____
_____

Appendix I
Corah's Dental Anxiety Scale

CORAH'S DENTAL ANXIETY SCALE

Code_____

PLEASE ANSWER THE FOLLOWING QUESTIONS BY CIRCLING THE ANSWER THAT BEST DESCRIBES HOW YOU FEEL.

1. If you had to go to the dentist tomorrow, how would you feel about it?
a) I would look forward to it as a reasonably enjoyable experience.
b) I wouldn't care one way or the other.
c) I would be a little uneasy about it.
d) I would be afraid that it would be unpleasant and painful.
e) I would be very afraid of what the dentist might do.

2. When you are waiting in the dentist's office for you turn in the chair, how do you feel?
a) Relaxed.
b) A little uneasy.
c) Tense.
d) Anxious.
e) So anxious that I sometimes break in a sweat or almost feel physically sick.

3. When you are in the dentist's chair waiting while she/he gets her/his drill ready to begin working on your teeth, how do you feel?
a) Relaxed.
b) A little uneasy.
c) Tense.
d) Anxious.
e) So anxious that I sometimes break in a sweat or almost feel physically sick.

4. You are in the dentist's chair to have your teeth cleaned. While you are waiting and the dentist is getting out the instruments, which she/he will use to scrape your teeth around your gums, how do you feel?
a) Relaxed.
b) A little uneasy.
c) Tense.
d) Anxious.
e) So anxious that I sometimes break in a sweat or almost feel physically sick.