Unique Protocol ID: LUI-S4

Brief Title: An Efficacy and Safety Trial of Intranasal Ketorolac in Emergency Department Patients for the Treatment of Acute Pain (Sprix)

Official Title: A Prospective, Open-label, Nonrandomized Efficacy and Safety Trial of Intranasal Ketorolac in Emergency Department Patients for the Treatment of Acute Pain

Protocol: Version 4.0/ September 21, 2011

Principal Investigator: Sharon E. Mace, MD

Sponsor: Luitpold Pharmaceuticals, Inc

PROTOCOL NUMBER 1

Clinical Study Protocol #S4

A Prospective, open-label, nonrandomized efficacy and safety trial of intranasal ketorolac in emergency department patients for the treatment of acute pain

Product:	Ketorolac (Sprix)
Version/Date:	Version 4.0/September 21, 2011
Study Design:	Prospective, open-label, nonrandomized efficacy and safety trial
Study Clinical Site	Cleveland Clinic 9500 Euclid Avenue, E-19 Emergency Services Institute Cleveland, Ohio 44195
Study's Principal Investigator	Sharon E. Mace, MD, FACEP, FAAP Professor of Medicine Cleveland Clinic Lerner College of Medicine, Case Western Reserve University

This study will be conducted in compliance with the protocol, Good Clinical Practice (GCP) Guidelines, and all other applicable regulatory components.

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BRIEF ABSTRACT

INTRODUCTION: Pain is a common reason for individuals to seek health care, especially emergency care. Ketorolac has numerous advantages over other pain medications, especially the opioids. The intranasal administration of ketorolac has been shown to be safe and effective in the treatment of postoperative pain following major abdominal surgery and post dental surgery, but there have been no studies evaluating the use of intranasal ketorolac for the treatment of acute pain in the emergency department.

METHOD: Twenty-five adults who are in the ED for an acute episode of pain will receive a single dose of intranasal ketorolac. Their pain before and after receiving the ketorolac will be measured by pain scales e.g. the numeric rating scale (NRS). The efficacy will be assessed by several measures including pain relief, pain intensity difference, global pain evaluation, global assessment of analgesia, and the summed pain intensity difference (SPID). This will allow for assessment of meaningful pain relief and the time to pain relief. The safety will be assessed by documentation of adverse events, vital signs, and clinical assessment of the nasal mucosa before and after the intranasal administration of the drug. The efficacy, tolerability and safety will also be assessed by patient and health care provider questionnaires.

PRIMARY OBJECTIVES: To determine the efficacy of ketorolac in an acute care setting, the emergency department (ED).

SECONDARY OBJECTIVES: To determine the safety and tolerability of ketorolac in an acute care setting, the ED.

PATIENT POPULATION: Adults: 18- 64 years of age, previously healthy men and nonpregnant women, with acute pain (e.g. an acute orthopedic injury such as a fracture or a kidney stone) being seen in the emergency department.

INTERVENTION: Single dose of intranasal ketorolac

CLINICAL MEASUREMENT: Pain scale (numeric rating scale = NRS) will be completed before and after giving intranasal ketorolac. Pain relief (e.g. numeric pain scale), global pain evaluation, pain intensity differences, global anesthesia (global pain relief) and patient/health care questionnaires will be completed.

OUTCOME: Decrease in pain by several measures including NRS after intranasal ketorolac is given, tolerability and safety evaluation

INTRANASAL KETOROLAC FOR THE TREATMENT OF ACUTE PAIN IN THE EMERGENCY DEPARTMENT

1. INTRODUCTION

1.1 Background

Pain is the number one reason for seeking health care. Patients are commonly seen in the emergency department (ED) with acute pain. Considering all ED visits, pain is the most common chief complaint. Up to 70% of ED visits are related to pain as the rationale for the ED visit.[1] Moreover, this does not include those individuals seeking care in urgent care centers, clinics or offices.

Ketorolac is effective in relieving pain. It has several advantages over other pain medications, including the opioids. First, since it does not bind to the opiate receptors (mu, kappa, and delta), it is nonaddicting. However, a 30 mg dose of ketorolac given intramuscularly has a demonstrated analgesic effect between that obtained with morphine 6 mg and 12 mg. Next, it also has the additional safety advantage in that it avoids the side effects of the opioids including the fact that it does not cause respiratory depression or hypotension.

The intranasal route of administration has numerous benefits over other methods of drug administration. The intravenous (IV) route of drug administration is painful, takes time to establish, costs more to administer, and can have an initial high peak of drug effect (Tmax) which can have unwanted side effects/complications (e.g. rapid peak with an increased possibility of complications such as hypotension and respiratory depression).[2] The intramuscular route is also quite painful.[2] Orally administered medications take time to be absorbed and exert a maximal effect, have a variable absorption from the gastrointestinal tract, and may not be an option in patients with vomiting, diarrhea, mal-absorption or other gastrointestinal disorders.[2]

The intranasal route is easy to administer, is nonpainful (unlike an intramuscular shot or IV line insertion), has a rapid onset, and a more level or consistent efficacy over time with less of a sudden peak than IV and likely, lesser side effects/complications than IV.

1. Mace SE, Murphy MF. Pain management and procedural sedation: definitions and clinical applications. In: Mace SE, Ducharme J, Murphy MF (eds). Pain management and Sedation: Emergency Department Management. 1st ed. New York: McGraw-Hill Co, 2006; Ch. 3, pp. 7-14.
2. Mace SE. Alternate routes for the systemic delivery of analgesics and sedatives. In: Mace SE, Ducharme J, Murphy MF (eds). Pain management and Sedation: Emergency Department Management. 1st ed. New York: McGraw-Hill Co, 2006; Ch. 47, pp. 366-380.

1.2 Summary of Clinical Studies with Intranasal Ketorolac

1. Singla N, Singla S, Moodie J, Brown C. Intranasal ketorolac for acute postoperative pain. Current Medical Research and Opinion 2010; 26(8): 1915-1923.

This was a double-blind, randomized controlled, multicenter (6 sites in the United States and New Zealand) trial in 321 adults (ages18 to 64 years) undergoing major open abdominal surgery under general anesthesia . Patients were randomized to receive either intranasal ketorolac 31.5 mg or placebo, administered as one spray (100 µL) into each nostril, every 6 hours for the first 48 hours following surgery, then up to four times a day. After surgery, patients received intravenous opioid until they were comfortable. Then pain intensity (PI) ratings using a visual analog scale (VAS) of 0 to 100 mm where 0 represents no pain and 100 is the worst pain imaginable were done. When PI ratings were at least 40 on the VAS, patients received either intranasal ketorolac or placebo; in addition to patient access to intravenous morphine via patient controlled analgesia (PCA) through at least 48 hours for pain not controlled by the study drug.

Results: Efficacy

Mean pain intensity VAS scores were significantly lower in the intranasal ketorolac group compared to placebo at 20 minutes (55.4 ± 1.9 vs. 60.5 ± 1.3, p=0.014), at 60 minutes (47.0 ± 1.5 vs. 53.5 ± 2.1, p= 0.008), 2 hours (43.3 ± 1.6 vs. 49 ± 2.2, p= 0.026), 3 hours (36.5 ± 1.5 vs. 44.2 ± 2.2, p= 0.002), 6 hours (29.8 ± 1.4 vs. 34.5 ± 2.2, p= 0.0038), 18 hours (29.0 ±1.5 vs. 32.3 ± 2.3, p= 0.016), 24 hours (26.4 ± 1.5 vs. 32.3 ± 2.3, p= 0.016), and 30 hours (24.3 ± 1.5 vs. 29.5 ± 2.2, p=0.037). The mean pain intensity difference (PID), calculated as the baseline VAS minus the post treatment VAS (PID = baseline VAS – post treatment VAS), was significantly higher for the ketorolac group than for the placebo at 20 minutes (p=0.010), 1 hour (p= 0.005), 2 hours (p= 0.034), and 3 hours (p= 0.017) The 6 hour summed pain intensity difference (SPID6) was significantly higher for the intranasal ketorolac group compared to the placebo group least square means (± SE) 117.4 (± 7.7) vs. 89.9 (± 10.6), p = 0.032; difference in means 27.6, (95% CI 2.5 – 52.7). The quality of analgesia was rated by patients (where 0 = poor, 1 = fair, 2 = good, 3 = very good, and 4 = excellent) as statistically better in the intranasal ketorolac group compared to the placebo group at all time points from 20 minutes to 24 hours except for the 40 minute and 6- hour time points. The global assessment of pain control was significantly better in the intranasal ketorolac group (where 0 = poor, 1 = fair, 2 = good, 3 = very good, and 4 = excellent), with the mean (± SE) being 2.6 (± 0.06) vs. 2.4 (± 0.09), p = 0. 009. The need for rescue medication was less for the intranasal ketorolac group than for the control. Morphine use was decreased by 34% for the 0 – 72 hours (82 mg vs.121 mg), although the difference was not statistically significant because of a decreased need for analgesia with the use of intranasal ketorolac. All of this data indicates better analgesia with intranasal ketorolac than for the placebo group

Results: Safety and Tolerability

The percent of patients with at least one adverse event were similar in the two treatment groups (ketorolac 93% (198/214) vs. placebo 96% (103/107). Adverse events were characteristic of those following major abdominal surgery. Common adverse events were nausea, constipation, vomiting, and headache. There was a trend (≥ 5% difference) for reduced incidences of nausea, constipation, pyrexia, and tachycardia in the ketorolac group compared to placebo. The majority of patients had mild adverse events with the proportion of adverse events similar in the ketorolac vs. the placebo group (84% vs. 79%). The rate of serious adverse events was identical at 6% in the two groups, of which 89% were considered not related to the study drug. Serious adverse events included: ileus, nausea and vomiting, post-procedural complications, and infections. No patient had gastrointestinal bleeding, surgical bleeding, or renal insufficiency considered related to the study drug.

Conclusion

Intranasal toradol was well-tolerated, provided effective pain relief within 20 minutes, and reduced the need for opioid analgesia use. "While intranasal ketorolac was assessed in an inpatient, conventional surgery setting in this study, intranasal ketorolac use may have more relevance for use in outpatient settings and ambulatory surgery or fast-track surgical procedures."

2. Grant GM, Mehlisch DR. Intranasal ketorolac for pain secondary to third molar impaction surgery: a randomized, double-blind, placebo-controlled trial. Journal Oral Maxillofacial Surgery 2010; 68: 1025-1031.

This was a single center, double-blind, randomized controlled trial of 80 adult patients (≥ 18 years of age) undergoing third molar impaction surgery. Patients were randomized to receive either intranasal ketorolac (31.5 mg) or intranasal placebo. Efficacy was measured using summed pain intensity difference (SPID) score over the first eight hours after dosing (primary efficacy variable), and secondary efficacy variables: pain intensity (visual analog scale = VAS) , total pain relief (TOTPAR) and global pain evaluation up to eight hours after dosing. Pain intensity was measured with a using a 100 mm VAS scale with 0 = no pain and 100 = worst pain possible. Pain intensity difference (PID) scores were calculated by subtracting each VAS post dose score from the baseline VAS score or PID = baseline VAS – post dose VAS. The SPID is calculated by taking a weighted sum of the PID scores.

The safety was assessed by assessing spontaneously reported adverse events and clinical signs, hematology and clinical chemistry throughout the treatment period and at a follow-up visit.

Results: Efficacy

The decrease in pain was significantly greater for the intranasal ketorolac than for the placebo. The results for intranasal ketorolac vs. intranasal placebo were mean (± SE) SPID8: 136.7 (± 33.0) vs. 105.2 (± 29.1), p< 0.001; SPID4: 90.3 (± 16.4) vs. 46.7 (± 13.5), p< 0.001; SPID6: 120.5 (± 24.7) vs. 76.7 (± 21.1), p < 0.001; TOTPAR4: 6.7 (±0.8) vs. 1.7 (± 0.4), p < 0.001; TOTPAR6 9.7 (± 1.2) vs. 2.4 (± 0.7), p < 0.001; TOTPAR8:12.0 (± 1.6) VS. 3.1 (± 0.9), p<0.001. The time to perceptible pain relief (time to onset in minutes) was 21.5 for intranasal ketorolac vs. 480 for intranasal placebo, p<0.001. The time to meaningful pain relief (time to onset in minutes) was 66.0 for intranasal ketorolac vs. 480 for placebo, p< 0.001. The need for rescue medication (minutes) was 360.0 for intranasal ketorolac vs. 95.5 for intranasal placebo, p< 0.001. The patient global assessment of pain control 8 hours after the intranasal ketorolac or placebo was also significantly better for ketorolac with a mean score of 1.9 ± 0.2 vs. 0.5 ± 0.1, p < 0.001.

Results: Safety and Tolerability

More adverse events were reported in the placebo group (8 patients with 10 events) than in the ketorolac group (3 patients with 3 events). All events were mild or moderate in severity and no serious events were reported. Headache occurred in 8 subjects (placebo n=5; ketorolac n=3) and was the only adverse event in the ketorolac group. In addition to the headache, 3 patients in the placebo group reported nausea, 1 had vomiting, and 1 had dizziness. There were no clinically relevant differences between the treatment groups in clinical assessments at the follow-up visit.

Conclusion

A single 31.5 intranasal dose of ketorolac provided rapid and effective pain relief and was well tolerated in oral surgery patients for up to 8 hours

3. Brown C., Moodie J, Bisley E, Bynum L. Intranasal ketorolac for postoperative pain: a phase 3, double-blind, randomized study. Pain Medicine. 2009; 10(6): 1106-1114.

This was a two hospital, phase 3, double-blind, randomized controlled study of 300 adults (N=199 Ketorolac, N= 101 placebo) undergoing surgery (abdominal or orthopedic or breast reconstruction surgery). Post-operative patients were randomized to either 30 mg (100 µl) intranasal ketorolac or intranasal placebo as a single dose or multidose regimen administered 3 times per day up to 5 days with backup analgesia as needed. Patients had access to morphine sulfate by patient-controlled analgesia (PCA). The primary efficacy endpoint was the single-dose summed pain intensity difference score (PID) at 6 hours. Secondary efficacy endpoints were pain intensity (PI) ratings using a visual analog scale (VAS) of 0- 100 mm where 0 represents no pain and 100 is the worst pain imaginable. PID scores were calculated by subtracting the post-treatment PI score from the baseline

score, where the baseline score was the PI rating made prior to the first dose of study medication on Day 1. SPID = Baseline PI – Post-treatment PI = Baseline VAS – Postreatment VAS. The summed PID (SPID) was determined from weighted PID scores over 6 hours, where the weight is proportional to the time elapsed since the previous rating. Secondary endpoints included onset, peak effect, quality of analgesia, and duration of analgesia in the first 6 hours after single dose study drug administration. Onset of analgesia was determined by the patients clicking a stopwatch at the time they reached "meaningful" pain relief, where meaningful relief was defined as "relief that definitely makes you feel better". Peak effect was the maximum PID score prior to restarting morphine sulfate by PCA. Quality of analgesia was rated using a five-point categorical scale where 0 = poor, 1= fair, 2 = good, 3 = very good, and 4 = excellent. The duration of analgesia was the time from the first dose of study medication on Day 1 to the first dose of morphine sulfate after restarting PCA. For the multidose regimen, efficacy assessments were global evaluation of pain control, mean total morphine sulfate use, and quality of analgesia ratings. The global assessment of pain control was rated by patients at the end of each day using a five-point categorical scale, where 0= poor, 1= fair, 2 = good, 3 = very good and 4 = excellent. Safety was assessed from spontaneously reported adverse events and measurement of adverse clinical signs. Hematology and clinical chemistry measurements were made at the termination visit, which occurred between 4 and 9 days after the start of dosing.

Results: Efficacy

The SPID6 score was significantly higher for the ketorolac group than for the placebo group. The mean (± SE) was 83.8 (± 10.6) for ketorolac vs. 37.2 (± 12.9) for the placebo $p= 0.007$. For the single-dose group, the mean PID scores through 6 hours were significantly higher for subjects in the ketorolac group than the placebo group at every time point (1/2, 1, 2, 3, 4 hours). Both the peak relief and the maximum PID score prior to restarting the PCA were significantly higher in the ketorolac group compared to the placebo group. For the single dose regimen, the quality of analgesia was significantly better for the ketorolac group compared to the placebo group at ½, 1, 2, 3, 4, and 5 hours and approached significance at 6 hours. The duration of analgesia was significantly longer in the ketorolac group vs. the placebo group, as denoted by the time to restarting PCA or requesting rescue medication (3 vs. 1.3 hours, $p < 0.04$). A significantly greater proportion of patients in the ketorolac group reported meaningful pain relief compared to placebo at 1 and 1.5 hours ($p< 0.05$) and approached statistical significance at 2 hours. Morphine use was significantly lower in the ketorolac group compared with the placebo group for all time intervals ($p< 0.001$). The mean (± SE) morphine use for ketorlac vs. placebo was 34.0 (±1.64) vs. 48.4 (± 2.93) on day 1, 18.8 (± 11.51) vs. 29.2 (± 2.61) for day 2, and 51.4 (± 2.75) vs. 774. (± 5.28) for days 1 and 2. The global pain assessment was significantly better for the ketorolac group than the placebo group on days 3 and 4. The quality of analgesia rating was significantly higher at the 8 hours in the ketorolac group vs. the placebo group at 8 hours: 2.9 (± 0.06) vs. 2.6 (± 0.1), $p= 0.011$).

Results: Safety

The rates of adverse events were similar in the two treatment groups (ketorolac 97.5% vs. placebo 98.0%) and were characteristic of events observed following major surgery and were not considered related to the study treatment in the majority 80%, (1150/1437) and were considered mild (72.9%). In the ketorolac group, nasal irritation (24.1% vs. 1.9%, p < 0.0001), throat irritation (7.0% vs. 0.9%) and lacrimation (7% vs. 0%) occurred more frequently in the ketorolac group than in the placebo group. Most events related to nasal irritation were mild, transient, and did not increase in severity with repeat dosing. Pyrexia was reduced in the ketorolac group (44% vs. 67%, P= 0.001). Serious adverse events were similar in both groups: 5 patients for ketorolac (2.5%), and 2 patients for placebo (1.9%). These were post –procedural hemorrhage (N=2), wound infection (N=1), wound complication (N=1), and wound secretion (N=1) for ketorolac and pain (N=1) and pleuritic pain (N=1) for placebo. The only serious event rated possibly related to study medication was the wound complication. There were no clinically relevant differences between the treatment groups regarding vital signs, hematology, or clinical chemistry measurements. No deaths occurred during the study.

Conclusion

Intranasal ketorolac was well tolerated and effective in treating moderate to severe postoperative pain in inpatients. The convenience of intranasal dosing suggests that its usefulness in the ambulatory care setting should be evaluated.

4. Moodie JE, Brown CR, Bisley EJ, Weber HU, Bynum L. The safety and analgesic efficacy of intranasal ketorolac in patients with postoperative pain. Anesthesia and Analgesia 2008; 107(6): 2025- 2031.

This was a single center, double-blind, randomized controlled study of 127 adult patients (N=42 placebo, N= 43 ketorolac 10 mg, N= 42 ketorolac 31.5mg) undergoing major surgery. Postoperative patients were randomized to either intranasal administration of placebo or ketorolac 10 mg or ketorolac 31.5 mg every 8 hours for 40 hours. The study drug was administered intranasally, giving 2 doses of 100 µL of the study drug, with 1 dose (100 µL to each nostril) via a metered device. Pain intensity was assessed after receiving the study drug. Patient controlled analgesia (PCA) was provided by supplemental morphine.
The subjects rated their pain on a 100 mm visual analogue scale (VAS) where 0= no pain and 100 = worst pain possible. The pain intensity difference (PID) was calculated by subtracting the post study drug VAS from the baseline (pre-study drug) VAS or PID = post- study drug VAS – baseline VAS. The summed PID (SPID) was calculated by adding the weighted PID scores over the time intervals.

Outcome measures: The primary outcome measure was the total morphine use by PCA pump in the first 24 hours. Secondary outcome measures were total morphine use for first 2 days (48 hours) and total morphine use on day 2 (24 to 48 hours)

Results: Efficacy

The analgesic response was significantly greater the for 31.5 mg ketorolac group compared with the placebo for day 1, day 2 and the 48-hour morphine use, and for the 4-hour and 6 hour SPID. The 10 mg ketorolac groups also demonstrated a better analgesic response than for the placebo, but the difference was not statistically significant. The mean morphine consumption for the 3 groups was day 1 post-op: placebo 56.5 mg, 10 mg ketorolac 54.3 and 31.5 mg ketorolac 37.8 mg (p=0.0013), day 2 placebo 32.6 mg, 10 mg ketorolac 28.3 mg, and 31.5 mg ketorolac 23.11 mg (p =0.0182), and for the 48 hours post-op: placebo 87.9 mg, 10 mg ketorolac 78.7 mg, and 31.5mg ketorolac 61.4 mg (p= 0.0060). The 4 hour SPID was 75.9, 10 mg ketorolac 89.6, and 31.5 mg ketorolac 120.1 (p = 0.0017). The 6 hour SPID was placebo 130.6, 10 mg ketorolac 154.8, and 31.5 mg ketorolac 195.5 (p=0.0015).

Results: Safety

The frequency of adverse events for the 3 groups was placebo 97.6%, 10 mg ketorolac 100%, and 31.5 mg ketorolac 95.2%. Most adverse events were mild or moderate. The most common adverse events were pyrexia and nausea, both occurring in 50.4% overall. Pyrexia was significantly less common (p= 0.0088) in the 31.5 mg ketorolac group than in the placebo group, with pyrexia reported in 33.5% of the 31.5 mg ketorolac group, in 55.8% of the 10 mg ketorolac group and in 61.9% of the placebo group. Tachycardia was significantly less frequent in the 31.5 mg ketorolac group than the placebo group (p= 0.0317). The frequency of tachycardia in the 3 groups was placebo 40.5%, 10 mg ketorolac group 16.3%, and 31.5 mg ketorolac group 19.0%, Pruritus was less frequent in the ketorolac groups than placebo but the difference was not statistically significant (p= 0.0790). The frequency of pruritus was placebo 23.8%, 10 mg ketorolac 18.6%, and 31.5 mg ketorolac 9.5%. Adverse events typically associated with NSAID use (i.e. abdominal pain, dyspepsia, hematemesis, fluid retention, and oliguria) were all reported by three or fewer subjects in each group. Nasal irritation was reported in the following frequencies: placebo 11.9% (5 subjects), 10 mg ketorolac group 14.0% (6 subjects), and 31.5 mg ketorolac group 16.7% (7 subjects). The frequency reported for epistaxis was placebo 2.4% (1 subject), 10 mg ketorolac 2.3% (1 subject), and 31.5 mg ketorolac 7.1% (3 subjects). All events were mild or moderate in intensity.

Conclusion

Intranasal ketorolac in a 31.5 mg dose demonstrated significant analgesic efficacy compared to placebo and 10 mg of ketorolac.

1.3.Risk – Benefit

Ketorolac has value as a medicine to relieve pain. Ketorolac has numerous advantages over other classes of analgesics, especially opioids. Since ketorolac does not bind to opiate receptors, it is nonaddicting and avoids the side effects of the opioids.[3] Therefore, some of the advantages include: lesser incidence of respiratory depression, lesser incidence of hypotension, lesser incidence of constipation, and no danger of addiction. Multiple studies have demonstrated the benefit of ketorolac as a medication to decrease

or eliminate pain. Ketorolac has been proven effective for pain relief, especially for certain types of pain; such as musculoskeletal pain, headaches and the pain from renal colic. In appropriate patients; ketorolac is a relatively safe drug for the treatment of pain.[4-6] Side effects and complications, such as gastrointestinal complaints (e.g. abdominal pain, dyspepsia, GI bleeding) and renal dysfunction (elevation of the BUN and creatinine) have been reported but with appropriate patient selection are uncommon or rare. The use of NSAIDS including ketorolac is not recommended in patients with active peptic ulcer disease, renal disease or at risk for renal failure due to volume depletion, cerebrovascular bleeding, hemorrhagic disorders, or those with a high risk of bleeding. With appropriate patient selection, ketorolac can be a safe and effective medication for the relief of pain.

3. Highlights of prescribing information. Distributed by American Reagant, Inc. Shirley, NY 1967.
4. Rainer TH, Jacobs P, Ng YC, et al. Cost-effectiveness analysis of intravenous ketorolac and morphine for treating pain after limb injury: double-blind, randomized controlled trial. BMJ 2000; 321:1247-1251.
5. Cordell WH. Renal (ureteral) colic. In: Mace SE, Ducharme J, Murphy MF (eds). Pain management and Sedation: Emergency Department Management. 1st ed. New York: McGraw-Hill Co, 2006; Ch. 36, pp. 261- 268.3.
6. Kelly A. Headaches. In: Mace SE, Ducharme J, Murphy MF (eds). Pain management and Sedation: Emergency Department Management. 1st ed. New York: McGraw-Hill Co, 2006; Ch. 38, pp. 261- 268.3, pp.279-285.

2. STUDY OBJECTIVES AND ENDPOINTS

2.1 Objectives

2.1.1 Primary Objective

To determine the efficacy of intranasal ketorolac (sprix) in decreasing the acute pain of patients in the emergency department (ED)

2.1.2 Secondary Objective

To determine the safety and tolerability of intranasal ketorolac (sprix) in decreasing the acute pain of patients in the emergency department (ED)

2.2 Variables

2.2.1. Primary Efficacy Variable

The primary efficacy variables are the pain measurements after the administration of the intranasal ketorolac (sprix) as compared with the baseline pain scales. Pain scales to be used are the Numeric Rating Scale (NRS) where 0 = no pain and 100 mm = worst pain possible and the global assessment of pain (using a 5 point Likert scale) and the global assessment of analgesia (pain relief) (using a 5 point Likert scale) (See appendix 1)

2.2.2 Secondary Efficacy Variable

The secondary efficacy variables are additional (calculated) pain measurements after the administration of the intranasal ketorolac (sprix). This will include the pain intensity difference (PID) and the summed pain intensity difference (SPID) (See appendix 1)

2.2.3 Safety Variables
2.2.3.1 Primary Safety Variables
The primary safety variables are the occurrence of adverse events (after the intranasal ketorolac has been administered)
2.2.3..2 Secondary Safety Variables
The secondary safety variables are the vital signs taken after the intranasal ketorolac has been administered. An additional secondary safety variable is the appearance of the nasal mucosa after the administration of the intranasal ketorolac, sprix.

3. INVESTIGATIONAL PLAN

3.1 Overall Study Design and Plan

This is a prospective, nonblinded, efficacy, safety and tolerability trial in non-geriatric adults (from age 18 to 64 years) who are in the emergency department (ED) being treated for moderate to severe acute pain (e.g. NRS ≥ 4 on a 0 to 10 NRS or ≥ 40 on a 0 to 100 NRS). Written consent is obtained from the patient. Eligible subjects will be enrolled.

3.2 Study Population

3.2.1 Description

Adult non-geriatric (ages 18 to 64 years) subjects who present to the emergency department (ED) in moderate to moderately severe acute pain (e.g. NRS ≥ 4 on a 0 to 10 NRS or ≥ 40 on a 0 to 100 NRS) from an acute illness or injury (such as a kidney stone or an acute musculoskeletal injury) are eligible for enrollment in the study

3.2.2 Inclusion Criteria

A patient is eligible for enrollment into the study if all of the following criteria (and none of the exclusion criteria) are met:

1. Patient is being seen in the emergency department (ED) in acute pain from an acute illness or injury (such as a kidney stone or an acute musculoskeletal injury)
2. Age ≥ 18 years and < 65 years
3. Stable patient with stable vital signs, including not in shock (systolic BP >90), not in respiratory failure, and not a multiple trauma patient
4. Mentally competent patient is able to understand the consent form
5. Baseline pain score is moderate to severe (e.g. on NRS ≥ 4 on a 0 to 10 NRS or ≥ 40 on a 0 to 100 NRS)

3.2.3. Exclusion Criteria

A subject will be excluded from the study if any of the following criteria are met:

1. Unstable patients
2. Multiple trauma patients
3. Patients with any allergies to ketorolac or any of the components in the nasal spray preparation
4. Patients with active peptic ulcer disease
5. Patients with a history of asthma, urticaria, or other allergic-type reactions after taking aspirin or other NSAIDS
6. Patients about to undergo major surgery
7. Patients with renal disease or at risk for renal failure due to volume depletion
8. Pregnant or nursing mothers
9. Patients with suspected or confirmed cerebrovascular bleeding, patients with hemorrhagic diathesis, incomplete hemostatis, and those at high-risk of bleeding
10. Patient with a nasal abnormality or illness that could affect the absorption of intranasal medication (such as: nasal discharge, rhinitis, acute upper respiratory infection, acute epistaxis, nasal polyp, nasal tumor)
11. Patient with any other contraindication to the use of Sprix, or in whom use of Sprix would not be consistent with the approved package insert

3.3 Rationale for Choice of Study Design and Population

This is a prospective efficacy, safety and tolerability trial in non-geriatric adults. Active treatment (a single dose of intranasal ketorolac) will be used. The population selected for this study, adult nongeriatric patients is a patient population that may benefit from the use of intranasal ketorolac. This is a population in whom intranasal ketorolac has been approved for use and in whom intranasal ketorolac has been shown to be safe and effective when used for other types of pain, specifically post-operative pain from major surgery and post-operative dental surgery. This is also a population in whom, other routes of administration of ketorolac, (e.g. intravenous, intramuscular and oral) have been shown to be efficacious and safe. Therefore, it seems highly likely that the intranasal form of ketorolac, in an appropriate dose of 30 mg will also be effective, safe and well tolerated.

4. STUDY TREATMENTS

4.1 Medication(s) for study treatment.

The following study treatments will be administered in this study:
Ketorolac Tromethamine (Sprix) Nasal Spray
Manufactured by Luitpold Pharmaceuticals

Subjects in the emergency department with acute pain will be administered a single dose of intranasal ketorolac as per standard application (see 4.2).

4.2 Method for Application of Ketorolac (Sprix) for the Treatment of Acute Pain

After identifying appropriate adult patients (see section 3.2), obtaining written consent (see section 9.3), and performing all pre-dose (baseline) pain assessments, ketorolac (Sprix) will be administered in the standard fashion.

A single dose of 31.5 mg will be administered with one 15.75 mg spray (in a metered dose of 100 µL per spray) in each nostril for a total of two intranasal sprays per patient that total 31.5 mg in 200 µL. Note: The time at which the second intranasal spray administration is completed is time 0. As stated above, the baseline pain assessments will be completed prior to the administration of the intranasal ketorolac (sprix).

4.3 Storage, Handling, and Administration

Current ICH GCP Guidelines requires the study investigator to ensure that study treatment (e.g. nasal spray bottles of sprix) deliveries from the Sponsor are received by a responsible person (e.g. research designee or pharmacist), and also ensure:

- The deliveries are recorded.
- The study treatment is handled and stored safely and properly.
- The study treatment is only dispensed to study subjects in accordance with the protocol.

The study treatment, intranasal ketorolac (sprix), will be stored in accordance to product labeling. Exposure to light, freezing and extreme heat should be avoided. It is recommended that the study treatments (e.g. unopened sprix) be stored between 36° F and 46°F (2°C and 8°C). During use, containers of Sprix Nasal Spray will be kept at controlled room temperature between 59°F and 86°F (15°C and 30°C), and out of direct sunlight. In this study, once a subject has received the intranasal ketorolac (sprix) spray, the bottle will be discarded. Each subject will receive the recommended dose of sprix (31.5 mg with one 15.75 mg spray in a metered dose of 100 µL per spray in each nostril for a total of two intranasal sprays [total of 200 µL] per patient from a new previously unused intranasal bottle of sprix. There will be only one use per bottle of sprix or one bottle of sprix per subject and there will be no other uses from the same intranasal spray bottle. Each patient will receive a single dose of intranasal ketorolac.

The study treatment (e.g. intranasal ketorolac or sprix) will be checked for expiration dates prior to use to ensure that expired product will not be used.

Study treatment inventory and accountability records will be kept by the study investigator or designee. Accountability will be documented throughout the study. The procedures below are mandatory:

The Investigator will not supply any study treatment to subject's not enrolled ion the study.

The research designee or pharmacist will store the study treatment (e.g. intranasal ketorolac: sprix) in a secure storage facility under controlled storage conditions, accessible only to persons authorized by the Investigator to dispense study treatment.

The research designee or pharmacist will maintain study inventory. The inventory will include a detailed accounting of materials received and dispensed to each subject.

At the conclusion of the study, a final study treatment inventory on the Treatment Accountability Log will be conducted and the results of this inventory will be recorded. It must be possible to reconcile delivery records with those of used and unused study treatment.

4.4 Packaging and Labeling

Intranasal ketorlac (sprix) is packaged in a nasal spray bottle that delivers a mist containing 15.75 mg in a metered dose of 100 µL per spray administered in each nostril for a total of two intranasal sprays per patient with 31.5 mg total drug administered per dose.

4.5 Study Treatment Accountability

The study investigator/designee will verify that study treatments are received intact and in the correct amounts. This verification will be documented by signing and dating the Treatment Accountability Log. An accurate running inventory of the study treatment will be kept by the Investigator /designee, and will include the type of study treatment and the date the study treatment was dispensed.

4.6 Treatment Compliance

The prescribing information for each study treatment of intranasal ketorolac (sprix) and any other treatments (including medication(s), dose(s), route, and time(s) administered) by any route of administration (intravenous, intramuscular, oral, etc.) ordered by the clinician, (such as: other pain medications, sedatives, etc.) will be recorded.

5. SCHEDULE AND DESCRIPTION OF STUDY PROCEDURES

Study procedures will be performed as outlined in Figure 1 and summarized in Part 3: Investigational Plan.

Signed informed consent must be obtained from the subject before any study-related procedures may be performed.
Details regarding the informed consent process are provided in Section 9.3.

5.1 Study Procedures

5.1.1 Pre-Study Period

5.1.1.1 Present to the Clinical Site

Adult (non-geriatric) subjects ages 18 to 64 years with an acute painful injury or illness (such as an acute isolated musculoskeletal injury or a kidney stone) being seen in the emergency department may be eligible for this study.

5.1.2 Informed Consent

The patient will be approached to determine his/her interest in this study. If a subject is interested in the study, written informed consent is obtained (section 9.3) and screening will begin.

5.1.3. Patient Screening and Subject Log

After the patient presents to the clinical site, the Investigator/designee may review the patient's charts. A unique screening number will be assigned to patients that have had their records reviewed. This screening number will be assigned according to the institution's policies and procedures and may not contain any information that may assist in identifying the patient. A Subject Log will be maintained by the research site.

5.1.3.1 Screening Assessments

The following screening assessments will be completed during screening and the findings will be recorded.

- Inclusion and exclusion criteria (Sections 3.2.2 and 3.2.3, respectively)

- Patient number assigned

- Demographic information

5.1.4 Study Treatment

Study treatment assessments will be performed during the time the patient is in the clinical site and will be performed, if indicated at specific times (see subsections below) The following information will be obtained and the findings will be recorded:

Study treatment assessments at specified times (baseline prior to administration and after administration of intranasal ketorolac [sprix]) including vital signs (baseline, before administration of intranasal ketorolac) and after administration of intranasal ketorolac (prior to the patient leaving the clinical site, e.g. emergency department).

- Pain assessments
- Patient/health care provider questionnaires will be done prior to the patient leaving the clinical site
- Any side effects/adverse events
- Vital signs

5.1.4.1 Site Assessment

Pre/Post Administration of Intranasal Ketorolac (Sprix): The Healthcare provider will examine the patient's nasal mucosa and document the findings (such as: redness, drainage) both before administration and after administration of the intranasal ketorolac (sprix). Note: Any subject with abnormalities of the nasal passageway such as purulent discharge or epistaxis will be excluded from participation in the study.

5.1.4.2 Study Pain Assessments

Study pain assessments will be done before and after the administration of the single dose of intranasal ketorolac (sprix). All patients will have a minimum of two pain scores (NRS): a baseline (pre administration of the intranasal ketorolac) and a post administration of intranasal ketorolac. The time that the pain score is done, whether at baseline or post intranasal administration of the ketorolac, will be recorded any time a baseline or post-treatment NRS pain score is done. A post-treatment NRS pain score will be done immediately prior to the patient leaving the ED and immediately prior to the patient receiving rescue medication (e.g. any additional pain medication or sedatives) with the time post-treatment to be recorded. Depending on the length of time the patient is in the ED, additional NRS pain sores will be done, if possible. While the patient is in the ED, additional NRS pain scores will be recorded at specified times after study drug administration; specifically, at 20 minutes, 40 minutes, 1 hour, 2 hours, 3 hours, 4 hours, 5 hours and 6 hours for as long as the patient remains in the clinical site, in addition to time 0 (baseline = before administration of the study drug). (See Appendix 1) The pain scores will be compared and analyzed for statistical significance comparing the baseline (pre-study drug administration) with the "post-study drug administration or "treatment" pain scores.

5.1.4.3 Study Questionnaires

Study Questionnaires will be done by the patient and the health care provider after administration of the study drug (intranasal ketorolac [sprix]), prior to the patient leaving the clinical site. (See Appendix 2)

5.1.4.4. Standard-of-Care Procedures: Pain Management

Patients may receive additional medications as part of their emergency department treatment including additional pain medications, such as opioids. Any additional medications administered will be recorded. The need for additional medications (including the drug administered, the dose, the time, and the route of administration) will

be recorded. The need for additional pain medications (or the lack of need for additional pain medications) may also be a secondary efficacy endpoint.

5.1.5 Description and Documentation of Study Procedures

5.1.5.1 Study Number

The subject will be assigned a study number. This will be recorded in a study log. This will maintain patient confidentiality and eliminate patient identifiers from the patient case report form.

5.1.5.2 Demographics

The subject's age, gender, race/ethnicity, will be recorded.

5.1.5.3 Medical History

Relevant medical history for each subject will be obtained in order to determine eligibility in the study. Eligibility will be noted.

5.1.5.3 Medications during the Study

All medications administered in the emergency department (drug name, dose, route and time of administration) including the study drug and additional pain medications will be recorded.

5.1.5.4 Intranasal Ketorolac (Sprix) Administration during the Study

Intranasal Ketorolac (Sprix) will be administered in the standard manner as per the protocol and manufacturer instructions.

5.1.6 Efficacy Assessments

5.1.6.1 Pain Assessments

Pain scores will be recorded and documented before administration of the intranasal ketorolac (sprix) for a baseline pain assessment and at specified intervals after the administration of intranasal ketorolac (sprix). Post-treatment pain scores will be recorded immediately prior to discharge from the ED and immediately prior to any rescue (e.g. pain or sedative) medication. Post treatment pain scores will be collected for as long as the patient is in the clinical site and will be at 20 minutes, 40 minutes, 1 hour and for 1 hour intervals post treatment up to 6 hours (e.g. at 1, 2, 3, 4, 5, and 6 hours) in addition to pain scores immediately prior to rescue medication and immediately prior to discharge from the ED. Pain assessments will be by the Numeric Rating Scale (NRS).where 0 = no pain and 100 = the worst pain imaginable. (See Appendix 1)

5.1.6.2. Patient Questionnaires

Patient questionnaires will be obtained after administration of the intranasal ketorolac (sprix) and prior to the patient leaving the clinical site. (See Appendix 2)

5.1.6.3 Health Care Provider's Questionnaire(s)

The health care provider questionnaires will be obtained after administration of the intranasal ketorolac (sprix) and prior to the patient leaving the clinical site. (See Appendix 2)

5.1.6.4 Safety Assessments

5.1.6.5 Site Assessments: Clinical

Site assessments (clinical) of the nasal passageways e.g. an examination of both nostrils) will be done before and after administration of the intranasal ketorolac (sprix). This will document that there is no changes in the nasal mucosa, etc. secondary to the administration of the intranasal drug (sprix).

5.1.6.6 Side Effects/Adverse Events

Any and all side effects/adverse effects will be documented on the case report form. The health care provider will determine whether the side effect/adverse event is or is not related to the intranasal ketorolac (sprix).

5.2 Protocol Deviations

No deviations to the inclusion/exclusion criteria are allowed in this study. All deviations will be recorded on the patient's chart and on the appropriate case report form.

5.3 Study Withdrawal Criteria

5.4 Discontinuation of Study Treatment/Early Release from the Study

A subject who is enrolled in the study and for whom study treatment is prematurely terminated will be considered to be discontinued from study treatment. After discontinuation/early release from the study, the subject will receive standard-of-care treatment as per the treating clinician. End of Study Efficacy and Safety assessments will be performed, if appropriate and whenever possible.

5.5 Withdrawal for the Study

A subject may be withdrawn from the study at any time for any reason and without penalty or prejudice. The following situations may be cause for a subject to be withdrawn from the study:

- Subject did not fulfill the inclusion or exclusion criteria.
- Subject experienced a significant complication, deemed due to the study treatment
- Subject developed an intercurrent illness, condition, or procedural complication that would interfere with continued participation
- Subject voluntarily withdrew consent/ authorization
- Subject was in violation of the protocol
- Treating health care provider (e.g. physician or mid-level provider) deemed it in the best medical interest of the subject to terminate involvement in the study at any time

Upon occurrence of a serious adverse event or intolerable adverse event, the principal investigator will be notified. If a subject is discontinued from study treatment due to a serious adverse event, the event will be followed until resolution. The investigational staff will record on the case report form the reason(s) for discontinuation.

5.6 Noncompliance/Replacement

Subjects who discontinue from the study prematurely will not be replaced.

6. DEFINITIONS AND DESCRIPTIONS OF ASSESSMENTS AND ENDPOINTS

6.1 Pharmacokinetic/Pharmacodynamic Endpoints and Assessments

No pharnmacokinetic/pharmacodynamic endpoints or assessments will be performed in this study.

6.2 Efficacy Variables

6.2.1 Primary Efficacy Variable

- The primary efficacy variable is the assessment of pain by the NRS after the administration of intranasal ketorlac (sprix).

6.2.2 Secondary Efficacy Variables

The secondary efficacy variables are the global pain assessment scores, the global assessment of analgesia (pain relief) scores, the patient questionnaire and the health care provider questionnaire which are completed before the patient leaves the clinical site (e.g. ED).

6.3 Safety Variables

6.3.1 Primary Safety Variable

The primary safety variables are the occurrence of adverse events (after the intranasal ketorolac has been administered).

6.3.2 Secondary Safety Variables

The secondary safety variables are the vital signs taken after the intranasal ketorolac has been administered. An additional secondary safety variable is the appearance of the nasal mucosa after the administration of the intranasal ketorolac and prior to the patient leaving the clinical site. The nasal mucosa (both sides) will be examined for any abnormalities such as erythema, discoloration, swelling, etc at baseline (prior to administration of the intranasal study drug, sprix), and after administration of the intranasal study drug, sprix).

6.3.3 Adverse Events

6.3.3.1 Definitions

An adverse event is defined as any untoward medical occurrence in a subject administered a study treatment and which did not necessarily have a causal relationship with the treatment. An adverse event could therefore, be any unfavorable and unintended sign, symptom, or disease temporally associated with the use of a study treatment, whether or not related to the study treatment.

For the purposes of this study, a treatment-emergent adverse event is defined as any adverse event that occurs during the emergency department visit and after administration of the intranasal ketorolac (sprix). The treating clinician should reflect whether the event was considered to be “possibly related” or “not related” to any protocol mandated procedures during the study.

6.3.3.2 Serious Adverse Event

A serious adverse event is any untoward medical occurrence that:

- Results in death
- Is life-threatening
- Results in persistent or significant disability/incapacity
- Results in a congenital anomaly or birth defect, or
- Requires non-illness or injury related (presenting condition) inpatient hospitalization or prolongation of existing hospitalization (hospitalization for treatment /observation/examination caused by an adverse event is considered to be a serious adverse event)

Important Medical Events:

Important Medical Events are defined as events that:

- may not result in death
- may not be life-threatening
- may not require hospitalization

These may be considered serious adverse, based upon appropriate medical judgment. These events may jeopardize the patient or subject and may require surgical intervention to prevent one of the outcomes listed in this definition (21 CFR 312.32)

6.3.3.3 Reporting

Any serious, adverse event will be reported immediately to the Institutional Review Board.

7. DATA ANALYSIS AND STATISTICAL METHODOLOGY

7.1 Planned Sample Size

Since this is a prospective, efficacy and safety trial, the planned enrollment is for 25 patients who will receive a single dose of intranasal ketorolac. This sample size provides 80% power to demonstrate that the mean pain intensity to demonstrate that the mean pain intensity difference (PID), (where the PID = post-treatment NRS – baseline NRS) differs from zero when the effect size is 0.56. The effect size was calculated as the mean PID divided by the standard deviation.

7.2 Efficacy

The pain scores pre and post-treatment (after administration of the intranasal ketorolac [sprix] will be compared. Pain scales are a continuous variable. Therefore, pain scales and other pain assessments (such as PID, SPID) (all continuous variables) will be compared using t-test or F-test.
The questionnaires (patient and health care provider) are discrete variables and will be compared using chi-square or Fischer's exact test.
Significance is at p= 0.05.

7.3 Safety

- Safety will be assessed by adverse events documented on the case report form.
- Safety will be assessed by clinical assessment including vital signs before and after administration of the study drug, intranasal ketorolac (sprix).
- Safety will also be assessed by clinical assessment of the nasal mucosa before and after administration of the study drug, intranasal ketorolac (sprix).

8. TERMINATION OF THE STUDY

The study will be terminated when 25 subjects are enrolled and all data is obtained and documented on the case report form. A statistical analysis will follow, an abstract for presentation will be submitted and a manuscript for publication in a peer reviewed medical journal will be written.

9. ADMINISTRATION AND REGULATORY CONSIDERATIONS

9.1 Prior to Initiation of the Study

All regulatory requirements prior to initiation of the study must be met. This includes institutional review board approval (see 9.2)

9.2 Institutional Review Board

Appropriate documentation will be submitted to the Cleveland Clinic Institutional Review Board. Written and electronic approval will be obtained from the Cleveland Clinic Institutional Review Board prior to initiating the study.

9.3 Informed Consent/Authorization

The appropriate Consent forms will be approved by the Cleveland Clinic Institutional Review Board prior to initiating the study.

9.4 Duties of the Investigator

The study investigator will comply with the requirements for human investigation as set forth by the Cleveland Clinic Review Board.

9.5 Monitoring

Monitoring and auditing by the Cleveland Clinic Institutional Review Board and other relevant regulatory authorities may occur. The confidentiality of the subject's identity will be protected according to regulations when source documents are accessed.

9.6 Study Records

- Inclusion and exclusion criteria information
- Participation in the study (signed and dated informed consent/authorization)
- Visit date
- Efficacy and safety data
- Adverse events, if any
- Premature discontinuation rationale, if applicable
- Completion or termination of the study

9.7 Records Retention

Appropriate records will be kept as per the Cleveland Clinic Institutional Review Board

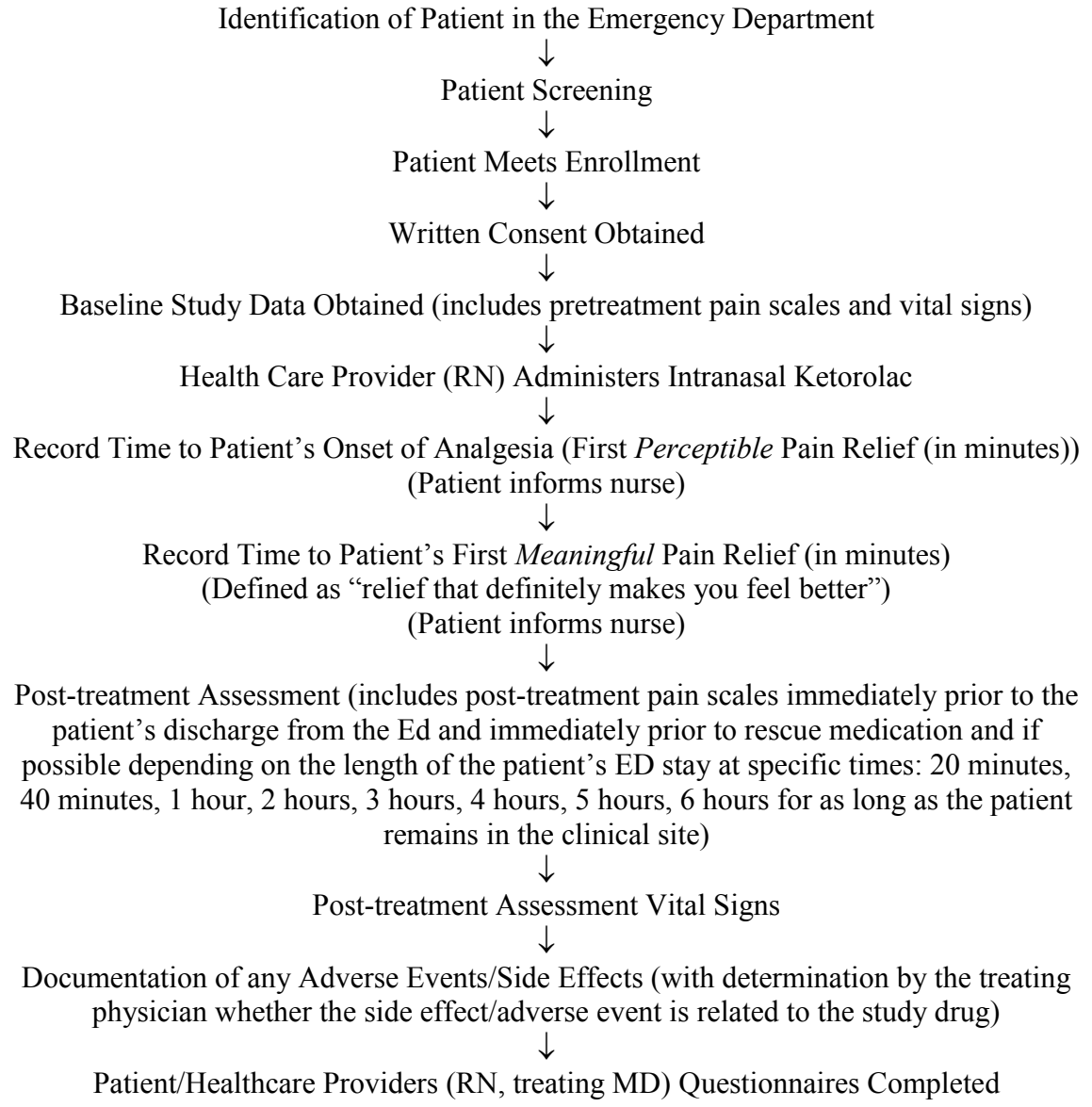
9.8 Subject Privacy/Authorization

Subject information obtained as a result of this study is considered confidential and disclosure to third parties is prohibited. Medical information may be assessed only after approval from the subject to the Investigator or to other appropriate medical personnel responsible for the subject's well being. The Sponsor will not disclose any confidential information regarding subjects during performance of study duties without justifiable reasons. The sponsor affirms the subject's right to protection against invasion of privacy. Only subject identification numbers and /or initials will identify subject data; however, the IRB, and regulatory authorities may have direct access to any study- related information. The HIPAA and PIPEDA Privacy Rule provides federal protection for the privacy of protected health information (PHI) by implementing standards to protect and guard against the misuse of individually identifiable health information of subjects participating in sponsored clinical trials. "Authorization'' is required from each subject participating in this study (i.e. specific permission granted by an individual to a covered entity for the use and disclosure of an individual's PHI). A valid authorization must meet the implementation specifications under the HIPPA/PIPEDA Privacy Rule. A valid authorization is available at the Cleveland Clinic.

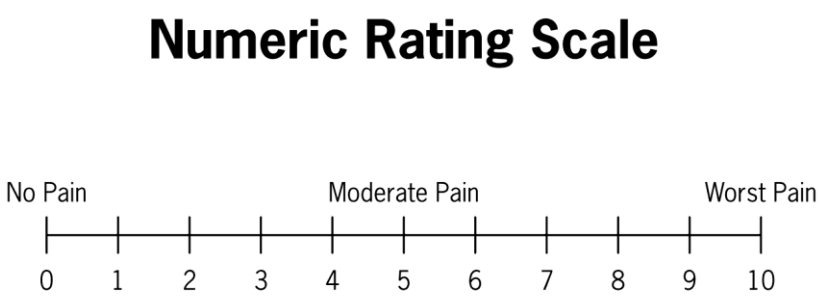
LIST OF FIGURES

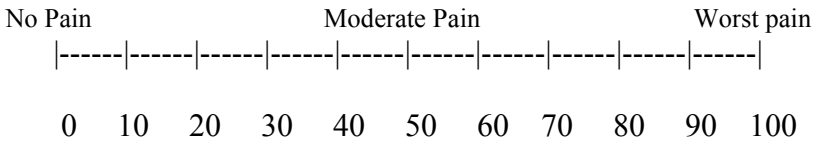
APPENDIX

Figure 1: Schematic Representation of Study Design



Appendix 1A: Numeric Pain Rating Scale





Appendix 1B: Global Pain Assessment Scale

How would you rate your pain?
0 = none 1 = a little (mild) 2 = some (moderate) 3 = severe
4 = very severe (extreme)

Appendix 1C: Global Assessment of Analgesia
(Global Assessment of Pain Relief)
How would you rate your pain relief?
0 = poor 1= fair 2= good 3 = very good 4 = excellent

Appendix 1D: Calculated Pain Assessments:
Pain Intensity Difference (PID)
Summed Pain Intensity Difference (SPID)
(Weighted Sum of PID)
Total Pain Assessment Relief (TOTPAR)
(Weighted sum of pain relief scores)

Appendix 2:Questionnaires

Appendix 2A: Patient Questionnaire

1. Did the intranasal pain medicine decrease your pain? yes_____ no_____
2. How effective was the intranasal pain medicine in decreasing your pain?
   Mild decrease in pain__ Moderate decrease in pain___ Strong decrease in pain____
3. How satisfied were you with the use of the intranasal spray?
   Very unsatisfied__ Unsatisfied____ Satisfied___ Very satisfied_____
4. Would you consider using this intranasal pain medicine in the future when you had pain? yes____ no_____

Appendix 2B: Health Care Provider Questionnaire

1. Was the patient successfully treated (had less pain) by using the spray?
   yes___ no___
2 Did the patient have any unacceptable side effects from use of the spray?
   yes__no___.
3. How satisfied How satisfied were you with the use of the intranasal spray?
   Very unsatisfied__ Unsatisfied____ Satisfied___ Very satisfied____
4. Would you consider using this intranasal pain medicine in the future for your patients who have acute pain? yes____ no_____