# Effect of NSAID Use on Pain and Opioid Consumption Following Distal Radius Fracture: A Prospective, Randomized Study

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## 1. Abstract

In the United States, drug overdose deaths and opioid-involved deaths continue to increase, quadrupling since 1999; six out of ten drug overdose deaths involve an opioid[1,2]. Overdoses from prescription opioids are a driving factor in the 15-year increase in opioid overdose deaths. The amount of prescription opioids sold to pharmacies, hospitals, and doctors' offices has drastically risen, yet there had not been an overall change in the amount of pain that Americans reported[1,3]. Deaths from prescription opioids—drugs like oxycodone, hydrocodone, and methadone—have more than quadrupled since 1999[4].

Non-steroidal anti-inflammatory drugs (NSAIDs) have been shown to control both postoperative pain and pain associated with some orthopaedic injuries in children and adults with certain orthopaedic injuries[5–9]. Further, the use of NSAIDs for pain control has been shown to lessen the use of narcotic pain medications, the adverse effects of which are well known[5,9–11]. With the current opioid epidemic, more research is needed to determine strategies to reduce opioid use in patients with orthopaedic injuries. Chapman et al. showed that NSAIDs can be used effectively to reduce postoperative pain and narcotic use in patients who had undergone carpal tunnel release[12]. Although distal radius fractures are one of the most common fractures, no studies have examined the effect of NSAIDs on distal radius fracture pain. The purpose of this study is to compare pain and narcotic pain medication use in patients who have had distal radius fractures in patients who use NSAIDs to those who do not.

To the authors' knowledge, there have been no clinical prospective, randomized studies to evaluate the effect that NSAIDs have on patients with distal radius fractures. We hypothesize that NSAID administration in the acute phase of distal radius fracture healing will be non-inferior for pain control and decrease the use of opioid analgesics compared to patients who take acetaminophen for pain control during this same time period. Furthermore, we hypothesize that patients will have similar or better patient reported outcomes, range of motion, and strength with the administration of NSAIDs.

## 2. Objectives

Primary Aims:

1. To compare postoperative pain of skeletally mature patients with distal radius fractures administered NSAIDs and acetaminophen for pain control versus those administered acetaminophen for pain control.
2. To compare the need for narcotic pain medication for breakthrough pain in patients given NSAIDs and acetaminophen for pain control as compared to patients given acetaminophen for pain control.

Secondary Aims:

1. To evaluate patient reported outcome scores, range of motion, strength, and complications in patients given NSAIDs and acetaminophen for pain control as compared to patients given acetaminophen for pain control
2. To compare the rate of non-union of distal radius fractures at 6 weeks in skeletally mature patients administered NSAIDs and acetaminophen for pain control versus those administered acetaminophen for pain control.

## 3. Background

In the United States, drug overdose deaths and opioid-involved deaths continue to increase, quadrupling since 1999; six out of ten drug overdose deaths involve an opioid[1,2]. Overdoses from prescription opioids are a driving factor in the 15-year increase in opioid overdose deaths. The amount of prescription opioids sold to pharmacies, hospitals, and doctors' offices

has drastically risen, yet there had not been an overall change in the amount of pain that Americans reported[1,3]. Deaths from prescription opioids—drugs like oxycodone, hydrocodone, and methadone—have more than quadrupled since 1999[4].

Non-steroidal anti-inflammatory drugs (NSAIDs) have been shown to control both postoperative pain and pain associated with many orthopaedic injuries in children and adults with certain orthopaedic injuries[5–9]. Further, the use of NSAIDs for pain control has been shown to lessen the use of narcotic pain medications, the adverse effects of which are well known[5,9–11]. With the current opioid epidemic, more research is needed to determine strategies to reduce opioid use in patients with orthopaedic injuries. Chapman et al. showed that NSAIDs can be used effectively to reduce postoperative pain and narcotic use in patients who had undergone carpal tunnel release[12]. Although distal radius fractures are one of the most common fractures, no studies have examined the effect of NSAIDs on distal radius fracture pain. The purpose of this study is to compare pain and narcotic pain medication use in patients who have had distal radius fractures in patients who use NSAIDs to those who do not.

## 4. Inclusion/Exclusion Criteria

Inclusion Criteria:

- Age ≥ 18
- Distal radius fracture

Exclusion Criteria:

- Contraindication to NSAID use
    1. Cannot tolerate
    2. Gastritis
    3. Ulcers
    4. Chronic kidney disease stage 4 or higher (i.e. GFR <30ml/min)
    5. Bleeding disorders/thrombocytopenia (platelet count <100,000)
- Inability to take breakthrough medications
- Regular use of NSAIDs
- Regular use of narcotics
- Open fracture
- Other orthopaedic injuries (polytrauma)
- Pathologic fracture
- Previous injury to the bone
- Pregnant or plan to become pregnant
- Unable to sign informed consent

## 5. Drugs

a. Ibuprofen, acetaminophen, and oxycodone are used in this study.
b. These drugs are commonly used for pain control. Ibuprofen and acetaminophen are available over the counter. Frequency of dosing is similar for ibuprofen and acetaminophen, which will reduce confounding variables for the study.
c. The drugs used in the study are FDA approved for their use in the study.

## 6. Enrollment/Randomization

Enrollment:

Patients who present to the University of Missouri Health Care Emergency Department (ED) or clinic with distal radius fractures will be screened for enrollment in the study. General inclusion/exclusion criteria will be used to determine patient eligibility. All eligible patients will be screened when they present to clinic for distal radius fracture. Patients who meet the

study criteria will be asked to participate in the study by study personnel. The study and all associated risks/benefits will be thoroughly explained to them. It will be clearly communicated to the patient that their participation is completely voluntary and they can withdraw from the study at any time, for any reason, with no effect to their care. The patient will be given adequate time to discuss their decision with family and friends, and ask the study staff questions. If the patient agrees, they will be asked to review/sign an informed consent document. If the patient signs the consent form, they will be provided with a copy of the signed document. We plan 200 subjects to complete the study. To account for attrition, we plan to enroll up to 250 patients in this study.

Randomization:
After informed consent is obtained, all patients who meet eligibility criteria will be randomized into one of two groups. Randomization will be achieved by using an excel formula to randomize all 250 patients to one of two groups. Randomization envelopes will then be labeled 1-250. Inside each envelope will be a piece of paper bearing a group name "NSAID" or "Control" depending on which group the subject number was randomized to in the excel document.

- Group 1: Control Group – will be administered acetaminophen for pain control with dose and frequency of 325mg 1-2 tablets q4-6h hours as needed, Maximum dose 1000mg. Maximum amount per day: 3g/day. Oxycodone 5mg 1-2 tablets q4-6 hours will be available as needed for breakthrough pain.

- Group 2: NSAID Group – will be administered ibuprofen 400-800 mg, up to three times a day and acetaminophen with dose and frequency of 325mg 1-2 tablets q4-6h hours as needed, Maximum dose 1000mg. Maximum amount per day: 3g/day as needed for pain control. Oxycodone 5mg 1-2 tablets q4-6 hours will be available for breakthrough pain.

## 7. Study Procedures

Screening/Randomization Visit: The screening visit will occur in the emergency room or in clinic, for every patient who agrees to participate in this study after they sign the consent and HIPAA documents, regardless on whether the fracture requires surgical intervention or not. All patients participating in this study will be randomized and assigned to either the "NSAID" or "Control" groups during this visit. In addition to this the following information will be collected:

- Age
- Gender
- Height
- Weight
- BMI
- Comorbidities
- Smoking status
- Date of injury
- Mechanism of injury
- AO classification of fracture
- VAS scores
- Pregnancy Status –
    - For female subjects, pregnancy status will verified by the resident verbally as per standard of care.

Operative Visit: Only patients clinically indicated to undergo surgery will have an operative visit. All fractures will be treated with standard of care in regards to operative treatment with volar locking plates with or without radial styloid pin(s). The patients may receive perioperative regional anesthesia based on the attending surgeon and anesthesiologist's discretion. Females of childbearing potential will undergo routine care pregnancy testing at surgery centers.

At Home: The participants will take ibuprofen or acetaminophen for pain control. They will also be given a prescription for oxycodone for breakthrough pain. The patient will be expected to record the patient's pain scores based on a visual analog scale and pain medication usage for up to four weeks after discharge from the Emergency Department and up to four weeks after surgery, if indicated.

Clinic Visits: The subject will be expected to follow up in clinic at 2 weeks, 6 weeks, 3 months and 6 months, and 1 year post-ED discharge or postoperatively. The 6 month and 1 year visit will be an online survey only. Each visit is described below.

- 2 weeks
    - Visual analog pain scale (VAS)
    - Radiographs of the affected extremity
    - Patient-reported outcome scores (Quick Disabilities of the Arm, Shoulder and Hand [QuickDASH], Patient-Reported Outcomes Measurement Information System [PROMIS])
    - Pinch and grip strength
    - Wrist range of motion (ROM)
- 6 weeks
    - Radiographs of the affected extremity
    - VAS
    - Patient-reported outcome scores (QuickDASH, PROMIS)
    - Pinch and grip strength
    - Wrist ROM
- 3 months
    - Radiographs of the affected extremity, if clinically indicated
    - VAS
    - Patient-reported outcome scores (QuickDASH, PROMIS)
    - Pinch and grip strength
    - Wrist ROM
- 6 months (survey only)
    - VAS
    - Patient-reported outcome scores (QuickDASH, PROMIS)
- 1 year (survey only)
    - VAS
    - Patient-reported outcome scores (QuickDASH, PROMIS)

Study Calendar:

| Procedures | Randomization | Operative Visit** | 2 weeks | 6 weeks | 3 months | 6 months | 1 year |
|---|---|---|---|---|---|---|---|
| **Visit #** | 1 | 2 | 3 | 4 | 5 | 6 | 7 |
| **Obtain informed consent** | X | | | | | | |
| **Assign Subject #** | X | | | | | | |
| **Inclusion/exclusion** | X | | | | | | |
| **BMI** | X | | | | | | |
| **Demographics** | X | | | | | | |
| **Co-Morbidities** | X | | | | | | |
| **Smoking Status** | X | | | | | | |
| **Date/Mechanism of Injury** | X | | | | | | |
| **AO Classification of fracture** | X | | | | | | |
| **Radiographs of the affected extremity** | X | | X | X | X | | |
| **Pinch and grip strength** | | | X | X | X | | |
| **Wrist range of motion (ROM)** | | | X | X | X | | |
| **Pain Assessment (VAS)** | X | X | X | X | X | X* | X* |
| **QuickDASH** | | | X | X | X | X* | X* |
| **PROMIS Surveys** | | | X | X | X | X* | X* |
| **AE/Complications** | X | X | X | X | X | X | X |

**Operative visit only for subjects with operative distal radius fractures X*=email survey only

## 8. Study Statistics

Primary outcome variables:

- A medication/pain diary will be collected to determine the number of oxycodone tablets used for breakthrough pain and number of ibuprofen or acetaminophen tablets
- Radiographic data will be collected to determine union at 6 weeks

Summary of data to be collected:

- Date of injury
- Age
- Gender
- Height
- Weight
- BMI
- Co-morbidities
- Smoking status
- Mechanism of injury
- AO classification of fracture
- VAS scores
- Grip strength
- ROM
- Outcome scores (QuickDASH, PROMIS)
- Complications

Statistical considerations:

- Sample size and power: Based on previous studies, we have conducted a power analysis and determined that the sample size of 200 is sufficient. The 200 total patients will be divided into two arms, 100 operative distal radius fractures and 100 non-operative distal radius fractures.
- Statistical analysis: To evaluate the effectiveness of randomization, patient characteristics will be compared between groups using standard statistical tests for

continuous data. Primary hypothesis of the study will be tested using standard statistical tests.

Early stopping rules:

- An interim analysis will be done after 50 patients have been randomized, treated, and released from hospital care. If the data from the interim analysis or from the adverse events occurring in the study reveal increased risks to the subjects or clearly demonstrate no benefit, then the study will be stopped for reevaluation, and the IRB notified immediately.

**9. Risks**

a. There are no additional risks associated with this study that are not part of the standard-of-care routine risks associated with treatment of these injuries.
b. These potential risks and/or discomforts associated with routine standard-of-care treatment of distal radius fractures and associated pain control can include the following:
    i. Constipation
    ii. Confusion
    iii. Nausea
    iv. Vomiting
    v. Abdominal pain
    vi. Dizziness
    vii. Respiratory depression
    viii. Acute renal insufficiency
    ix. Bleeding
    x. Infection
    xi. Nerve or blood vessel injury
    xii. Need for surgery/additional surgery
    xiii. Nonunion/malunion
c. Breach of Confidentiality Risk:
    i. Because patient data is being collected there is a slight risk of a breach of confidentiality.
d. To reduce this risk, most study data will be maintained in a password protected secure database, which only research staff have access to. Any physical study forms (ex. consent documents, screening forms, surveys) will be kept in a locked cabinet. All study data will be maintained for the minimum amount of time required by the University of Missouri.
e. Patient safety will be ensured through extensive post-operative monitoring to address patient complaints, assess for adequate pain control, monitor fracture healing, and allow for the collection of data. Adverse events will be reported to the IRB per federal guidelines. An interim analysis will be done after 50 patients have been randomized, treated, and released from hospital care. If the data from the interim analysis or from the adverse events occurring in the study reveal increased risks to the subjects or clearly demonstrate no benefit, then the study will be stopped for reevaluation, and the IRB notified immediately.
f. Study Withdrawal by Patient-Participation in this study is voluntary. If the study participant wishes to be withdrawn from the study following consent, they may do so by letting the key study personnel know they withdraw their consent.

## 10. Benefits

a. The potential benefits of this study lie in determining the effect, if any, that NSAIDs have on acute distal radius fracture healing in regards to rate of non-union or delayed union. If the study's hypothesis is correct, that the use of NSAIDs for pain control in acute distal radius fractures does not delay bone healing, this will offer an option for physicians to utilize that avoids the undesirable side effects of narcotic pain medications such as nausea, vomiting, constipation and sedation.
b. This project will help the medical community understand how the use of NSAIDs effect pain and opioid consumption following distal radius fractures. Information gained from this research project may help guide future practice protocols.

## 11. Costs

a. There is no additional cost to the patient
b. The patient will not be paid for participation in the study

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