Post-operative Pain Management in Supracondylar Humerus Fractures: A Randomized, Doubleblinded, Prospective Study

NCT04905563

Study Protocol and Statistical Plan

05/05/2021

Protocol

1. Purpose: The purpose of this study is to determine if scheduled nonsteroidal anti-inflammatory drugs (NSAIDs) provide equal or better pain control compared to scheduled opioids (standard of care) post-operatively in pediatric patients with SCHFs undergoing CRPP.

2. Background: Supracondylar humerus fractures (SCHFs) are the most common pediatric elbow fracture in children ages five to seven years old. Treatment is dependent on the type of fracture, but often includes surgical intervention with a closed reduction and percutaneous pins.

Pain following an orthopedic injury is most severe in the first forty-eight hours and is often undertreated in both children and adults (Clark, Plint, Correll, Gaboury, & Passi, 2016; Lim, 2015). Several studies have compared acetaminophen, ibuprofen and codeine for postoperative pain control in children; however, to our knowledge, there is limited research directly comparing scheduled acetaminophen and ibuprofen to scheduled acetaminophen-hydrocodone for postoperative pain control in children with supracondylar humerus fractures (SCHFs) undergoing a closed reduction percutaneous pinning (CRPP). A study conducted by Swanson, Chang, Schleyer, Pizzutillo and Herman (2012) compared acetaminophen to acetaminophen/codeine in children with type two and type three SCHFs and found decreased pain scores in the children treated with acetaminophen, although not statistically significant. Lim conducted a study in 2015 in which children were randomized into two groups following a fracture to an extremity. Group 1 received intravenous morphine for postoperative pain and Group 2 received ibuprofen for postoperative pain. Both groups received acetaminophen for breakthrough pain. Children in both groups had adequate pain control, but there was no statistical difference between the two. In a study by Morris, Stulberg, Stevemer and Kickner (2010), pediatric patients with simple fractures that did not require reduction or manipulation were given ibuprofen or acetaminophen with codeine. Pain control was equivalent between the groups; however, children preferred ibuprofen over acetaminophen-codeine, which allowed them to return to play faster and eating sooner. Additionally, researchers followed the patients' charts for four years and found no increased risk of fracture or delay in healing in the ibuprofen group. Clark, Plint, Correll, Gaboury and Passi found that ibuprofen significantly decreased pain at 60, 90 and 120 minutes following an acute orthopedic injury compared to acetaminophen or codeine (2016).

3. Inclusion Criteria: Children ages 4-13 years old with an isolated supracondylar humerus fracture (SCHF), extension and flexion type, undergoing closed reduction with percutaneous pinning (CRPP). Exclusion Criteria: Allergies to acetaminophen, ibuprofen, and/or acetaminophen-HYDROcodone. Liver or renal disease, history of bleeding disorder, medical diagnosis of juvenile arthritis, on chronic NSAIDs or Opioids PRIOR to the procedure, medical diagnosis of coagulopathies, open fractures, other injuries at time of diagnosis (multi-system trauma), vascular compromise and/or compartment syndrome upon admission, any patient/family who does not speak English.

4. Design: Randomized, double blinded, prospective study during the time period of 4/01/2019 to 12/31/2024

5. Protocol: Informed consent will be obtained prior to treatment. Informed consent will occur in the clinic, the emergency department, or the preoperative department, and will not delay the treatment of the subjects. Subjects will be randomly assigned to one of two groups: Group A (treatment) receives scheduled acetaminophen and ibuprofen and Group B (control) receives scheduled acetaminophen-hydrocodone (standard of care). Prior to surgery, pain for all participants will be controlled with IV Morphine 0.1 mg/kg/dose every two hours as needed. Post-operatively, patients in the NSAID group will receive acetaminophen 15 mg/kg/dose and ibuprofen 10 mg/kg/dose every six hours with a max dose of 650 mg/dose of acetaminophen and 600 mg/dose of ibuprofen. Patients in the opioid group will receive

acetaminophen-hydrocodone 0.15 mg/kg/dose every six hours with a max dose of 10 mg/dose. All medications will be drawn up by a pharmacist in opaque bottles to look the same, be the same volume, be the same color. All medications will be flavored with cherry syrup. A master list of subjects and the medications given will be kept in a password protected spreadsheet in the pharmacy. The total volume of all medications will be determined by the pharmacist and dependent on the patient's weight with a max volume of 40 milliliters (Figure 1). Post-operatively, all participants in this study will receive IV Morphine for breakthrough pain (standard of care) in addition to the scheduled medications they were randomly assigned to. Pain scores (standard of care) will be documented in the patient's electronic medical record (EMR) by the bedside nurse every two hours, prior to administration of pain medication and thirty minutes after administration of pain medication using the Wong-Baker Faces Pain Scale. Patients can receive IV Morphine for breakthrough pain after sixty minutes of receiving oral pain medications if their pain is not adequately controlled. All patients who experience emesis within thirty minutes of receiving oral pain medications will be given an additional dose of their oral medications (per standard of care). Upon discharge, patients will be given a prescription for acetaminophen-hydrocodone 0.15 mg/kg/dose and ibuprofen 10 mg/kg/dose, which is standard of care at LeBonheur. Follow up email/text will be done 48-72 hrs post- discharge from hospital via Twilio.

Perioperative steroids for this procedure are not used by the surgeons involved.

Surgery scheduling for these patients varies due to patient NPO status, OR availability, surgeon availability, and time of presentation.

If a patient received ibuprofen prior to presentation, they still may be randomized to either treatment group.

Acetaminophen and ibuprofen will be administered simultaneously, not in separate syringes.

Patients receiving the experimental treatment needing 2 consecutive doses of break through medicines for pain control will be switched to standard of care medicine. All nurses who staff the orthopedic floor will be trained by the PI (who is the nurse practitioner for the orthopedic service) on this and all procedures listed in the study protocol.

Figure 1

Weight Based Volumes

Weight	Volume
10-14.9 kg	15 mL
15-19.9 kg	20 mL
20-24.9 kg	25 mL
25-29.9 kg	30 mL
30-34.9 kg	35 mL
35+ kg	40 mL

6. Outcome Measures: Pain, amount of narcotics used, amount of NSAID used, total morphine equivalents, cost, length of stay, side effects of medications.

References

World Health Organization (WHO)- Analgesia Ladder 2018

National Institute on Drug Abuse. Opioid Overdose Crisis. http://www.drugabuse.gov

Swanson, Chang, Schleyer, Pizzutillo, & Herman. (2012). Postoperative pain control after supracondylar humerus fracture fixation. Journal of Pediatric Orthopaedics, 32(5).

Lim (2015). Postfracture pain relief in children can be adequately managed with ibuprofen. BMJ, 20(3).

Poonai, Bhullar, Lin, Papini, Mainprize, et. al. (2014). Oral administration of morphine versus ibuprofen to manage postfracture pain in children: a randomized trial. CMAJ, 186(18).

Morris, Stulberg, Stevemer, & Kicker (2010). Fracture pain relief for kids? Ibuprofen does it better. The Journal of Family Practice, 59(5).

Shephard & Aickin (2009). Paracetamol versus ibuprofen: A randomized controlled trial of outpatient analgesia efficacy for paediatric acute limb fractures. Pediatric Emergency Medicine, 21.

Cappello, Nuelle, Katsantonis, Nauer, Lauing, et. al. (2013). Ketoralac administration does not delay early fracture healing in a juvenile rat model. Journal of Pediatric Orthopaedics, 33(4).

Ali, Drendel, Kircher, & Beno (2010). Pain management of musculoskeletal injuries in children: Current state and future directions. Pediatric Emergency Care, 26(7).

Clark, Plint, Correll, Gaboury, & Passi (2016). A Randomized, Controlled Trial of Acetaminophen, Ibuprofen, and Codeine for Acute Pain Relief in Children with Musculoskeletal Trauma. PEDIATRICS, 119(3).

Koller, Myers, Lorenz, & Godambe (2007). Effectiveness of Oxycodone, Ibuprofen, or the Combination in the Initial Management of Orthopaedic Injury-Related Pain in Children. Pediatric Emergency Care, 23(9).

Statistical Analysis Plan (SAP):

We intend to examine the difference in pain scores between two groups of children for postoperative orthopedic pain using a two sided Mann-Whitney-Wilcoxon test. Additionally, we plan to use mixed linear regression model to consider between-group differences in pain score across all the time points. We will also compare medication usage, cost, length of stay, and side effects between the two groups.

In addition to testing each variable individually, we plan to use multivariate analysis techniques like multivariate analysis of variance (MANOVA) or multivariate regression can be used to simultaneously assess the effects of multiple variables while controlling for overall type I error.

The plan is to conduct two-sided Mann-Whitney-Wilcoxon test and the critical assumptions necessary to be verified were (1) Ensuring the comparability of the variable under examination across the two groups, necessitating it to be continuous, (2) Affirming the non-normal or skewed distribution of the data, (3) Confirming the independence of the samples, which were selected randomly, (4) Ensuring similarity in the distribution shapes of the data across both groups, notwithstanding the assumption that neither group's data adhered to a normal distribution.