

# **Comparison of Ketorolac at Three Doses in Children with Acute Pain: A Randomized Controlled Trial (KETODOSE TRIAL)**

Mohamed Eltorki, Redjana Carciumaru, Samina Ali, Anne Holbrook, Karen Beattie, Michael Livingston, Samira Samiee-Zafarghandy, Lehana Thabane, Lucia Giglia

Submitted to: JMIR Research Protocols  
on: April 25, 2025

**Disclaimer:** © The authors. All rights reserved. This is a privileged document currently under peer-review/community review. Authors have provided JMIR Publications with an exclusive license to publish this preprint on its website for review purposes only. While the final peer-reviewed paper may be licensed under a CC BY license on publication, at this stage authors and publisher expressly prohibit redistribution of this draft paper other than for review purposes.

Table of Contents

Original Manuscript..... 5

Supplementary Files..... 33

    Multimedia Appendixes ..... 34

        Multimedia Appendix 1..... 34



# Comparison of Ketorolac at Three Doses in Children with Acute Pain: A Randomized Controlled Trial (KETODOSE TRIAL)

Mohamed Eltorki<sup>1</sup> MBChB, MSc; Redjana Carciumaru<sup>2</sup> MD, MSc; Samina Ali<sup>3</sup> MDCM; Anne Holbrook<sup>4</sup> PharmD, MD, MSc; Karen Beattie<sup>5</sup> PhD; Michael Livingston<sup>6</sup>; Samira Samiee-Zafarghandy<sup>5</sup>; Lehana Thabane<sup>7</sup> PhD; Lucia Giglia<sup>5</sup> BSc, MSc, MD

<sup>1</sup>Pediatrics Cumming School of Medicine University of Calgary Calgary CA

<sup>2</sup>McMaster University Hamilton CA

<sup>3</sup>Pediatrics Faculty of Medicine University of Alberta Calgary CA

<sup>4</sup>Medicine Faculty of Health Sciences McMaster University Hamilton CA

<sup>5</sup>Pediatrics Faculty of Health Sciences McMaster University Hamilton CA

<sup>6</sup>Surgery Faculty of Health Sciences McMaster University Hamilton CA

<sup>7</sup>Biostatistical Unit St. Joseph's Research Institute St. Joseph's Hospital Hamilton CA

## Corresponding Author:

Mohamed Eltorki MBChB, MSc  
Pediatrics  
Cumming School of Medicine  
University of Calgary  
2500 University Dr NW  
Calgary  
CA

## Abstract

**Background:** Intravenous ketorolac is a potent non-opioid analgesic commonly used to treat moderate to severe pain in children and adults. Despite its widespread use in pediatric emergency settings, ketorolac dosing in children remains "off-label," with limited high-quality evidence to guide practice. Pharmacokinetic differences between children and adults suggest that lower ceiling doses adopted from adult practice may lead to suboptimal analgesia in pediatric populations. Inconsistent ketorolac dosing practices across centers reflect substantial clinical uncertainty. Amid efforts to reduce opioid use and provide effective non-opioid alternatives, rigorous pediatric trials evaluating ketorolac dosing are urgently needed.

**Objective:** The primary objective is to determine whether two lower-dose intravenous ketorolac strategies (0.25 mg/kg up to 30 mg or 0.5 mg/kg up to 10 mg) are non-inferior to the standard dosing regimen (0.5 mg/kg up to 30 mg) in reducing mean pain scores at 60 minutes post-administration in children aged 6–17 years presenting with moderate to severe pain. The secondary hypothesis is that ketorolac 0.5 mg/kg up to 10 mg will be superior to 0.25 mg/kg up to 30 mg by at least the minimally important difference (MID) of 2.0 points on the verbal Numerical Rating Scale (vNRS).

**Methods:** The KETODOSE trial is a single-center, randomized, double-blind, double-dummy, non-inferiority trial conducted at McMaster Children's Hospital. Eligible participants aged 6 to <18 years with moderate to severe pain (vNRS >4) are randomized in a 1:1:1 ratio to standard dosing or one of two low-dose ketorolac regimens. Study drugs are administered via IV push over 5 minutes. Pain scores are assessed at baseline, 30, 60, 90, and 120 minutes, and at 6 hours if still hospitalized. The primary endpoint is the mean change in vNRS score at 60 minutes. Secondary outcomes include pain scores at other time points, time to effective analgesia, rescue analgesia requirements, opioid consumption, and adverse events. Caregiver perceptions regarding analgesic use are evaluated using a mixed-methods semi-structured survey. A sample size of 180 participants (60 per group) provides 80% power to detect non-inferiority within a margin of 1.0 on the vNRS, assuming a standard deviation of 1.5. Intention-to-treat and per-protocol analyses will be performed.

**Results:** Recruitment is ongoing. Final analyses will be performed once follow-up is completed for all participants. Results will be disseminated through peer-reviewed publications, conference presentations, caregiver- and clinician-facing educational tools, and national knowledge mobilization networks.

**Conclusions:** The KETODOSE trial will provide urgently needed evidence to guide ketorolac dosing for acute pain in children.

If lower-dose regimens are shown to be non-inferior to standard dosing, this may promote safer prescribing practices, reduce adverse events, and support efforts to minimize pediatric opioid use, thereby improving acute pain management in pediatric emergency care. Clinical Trial: ClinicalTrials.gov NCT05641363

(JMIR Preprints 25/04/2025:76554)

DOI: <https://doi.org/10.2196/preprints.76554>

## Preprint Settings

1) Would you like to publish your submitted manuscript as preprint?

✓ **Please make my preprint PDF available to anyone at any time (recommended).**

Please make my preprint PDF available only to logged-in users; I understand that my title and abstract will remain visible to all users.

Only make the preprint title and abstract visible.

No, I do not wish to publish my submitted manuscript as a preprint.

2) If accepted for publication in a JMIR journal, would you like the PDF to be visible to the public?

✓ **Yes, please make my accepted manuscript PDF available to anyone at any time (Recommended).**

Yes, but please make my accepted manuscript PDF available only to logged-in users; I understand that the title and abstract will remain visible to all users.

Yes, but only make the title and abstract visible (see Important note, above). I understand that if I later pay to participate in <https://preprints.jmir.org/preprint/76554>

No. Please do not make my accepted manuscript PDF available to anyone. I understand that if I later pay to participate in <https://preprints.jmir.org/preprint/76554>

## Original Manuscript

Comparison of Ketorolac at Three Doses in Children with Acute Pain: A Randomized  
Controlled Trial (**KETODOSE TRIAL**)

Mohamed Eltorki, MBChB, MSc<sup>a,b</sup>, Redjana Cariumaru, MD, MSc<sup>b</sup>, Samina Ali, MDCM<sup>c</sup>, Anne Holbrook, PharmD, MD, MSc<sup>d</sup>, Michael Livingston, MD, MSc<sup>e</sup>, Samira Samiee-Zafarghandy, MD<sup>f</sup>, Karen Beattie, PhD<sup>g</sup>, Lehane Thabane,<sup>b,h</sup> Lucia Giglia, BSc, MD, MSc<sup>i</sup>

<sup>a</sup> Department of Pediatrics, Cumming School of Medicine, University of Calgary, Calgary, Alberta, Canada. <sup>b</sup> Department of Pediatrics, Faculty of Health Sciences, McMaster University, Hamilton, Ontario, Canada <sup>c</sup> Department of Pediatrics, Faculty of Medicine and Dentistry, University of Alberta, Edmonton, Alberta, Canada <sup>d</sup> Department of Medicine, Faculty of Health Sciences, McMaster University, Hamilton, Ontario, Canada <sup>e</sup> Department of Surgery, Faculty of Health Sciences, McMaster University, Hamilton, Ontario, Canada <sup>f</sup> Department of Pediatrics, Faculty of Health Sciences, McMaster University, Hamilton, Ontario, Canada <sup>g</sup> Department of Pediatrics, Faculty of Health Sciences, McMaster University, Hamilton, Ontario, Canada <sup>h</sup> St. Joseph's Research Institute, Biostatistical Unit, Hamilton, Ontario, Canada <sup>i</sup> Department of Pediatrics, Faculty of Health Sciences, McMaster University, Hamilton, Ontario, Canada

## **ABSTRACT**

### **Background:**

Intravenous ketorolac is a potent non-opioid analgesic commonly used to treat moderate to severe pain in children and adults. Despite its widespread use in pediatric emergency settings, ketorolac dosing in children remains "off-label," with limited high-quality evidence to guide practice. Pharmacokinetic differences between children and adults suggest that lower ceiling doses adopted from adult practice may lead to suboptimal analgesia in pediatric populations. Inconsistent ketorolac dosing practices across centers reflect substantial clinical uncertainty. Amid efforts to reduce opioid use and provide effective non-opioid alternatives, rigorous pediatric trials evaluating ketorolac dosing are urgently needed.

### **Objective:**

The primary objective is to determine whether two lower-dose intravenous ketorolac strategies (0.25 mg/kg up to 30 mg or 0.5 mg/kg up to 10 mg) are non-inferior to the standard dosing regimen (0.5 mg/kg up to 30 mg) in reducing mean pain scores at 60 minutes post-administration in children aged 6–17 years presenting with moderate to severe pain. The secondary hypothesis is that ketorolac 0.5 mg/kg up to 10 mg will be superior to 0.25 mg/kg up to 30 mg by at least the minimally important difference (MID) of 2.0 points on the verbal Numerical Rating Scale (vNRS).

### **Methods:**

The KETODOSE trial is a single-center, randomized, double-blind, double-dummy, non-inferiority trial conducted at McMaster Children's Hospital. Eligible participants aged 6 to <18 years with moderate to severe pain (vNRS >4) are randomized in a 1:1:1 ratio to standard dosing or one of two low-dose ketorolac regimens. Study drugs are administered via IV push over 5 minutes. Pain scores are assessed at baseline, 30, 60, 90, and 120 minutes, and at 6 hours if still hospitalized. The primary endpoint is the mean change in vNRS score at 60 minutes. Secondary outcomes include pain scores at other time points, time to effective analgesia, rescue analgesia requirements, opioid consumption, and adverse events. Caregiver perceptions regarding analgesic use are evaluated using a mixed-methods semi-structured survey. A sample size of 180 participants (60 per group) provides 80% power to detect non-inferiority within a margin of 1.0 on the vNRS, assuming a standard deviation of 1.5. Intention-to-treat and per-protocol analyses will be performed.

### **Results:**

Recruitment is ongoing. Final analyses will be performed once follow-up is completed for all participants. Results will be disseminated through peer-reviewed publications, conference presentations, caregiver- and clinician-facing educational tools, and national knowledge mobilization networks.

### **Conclusions:**

The KETODOSE trial will provide urgently needed evidence to guide ketorolac dosing for acute pain in children. If lower-dose regimens are shown to be non-inferior to standard dosing, this may promote safer prescribing practices, reduce adverse events, and support efforts to minimize pediatric opioid use, thereby improving acute pain management in pediatric emergency care.

### **Trial**

ClinicalTrials.gov NCT05641363

### **Registration:**

**BACKGROUND:**

Ketorolac tromethamine is a well-known non-opioid IV analgesic commonly used in children and adults for moderate to severe pain.<sup>1-3</sup> It is a nonsteroidal anti-inflammatory drug (NSAID) that inhibits the synthesis of inflammatory endogenous substances such as prostaglandins and thromboxanes. Ketorolac has been shown to provide similar analgesia to opioids after outpatient surgical procedures associated with moderate pain, such as fractures, hernia repair and tonsillectomy.<sup>1,4</sup> Ketorolac is commonly used in the Emergency Department (ED) for renal colic, abdominal pain, chest pain and migraine headaches.<sup>5</sup> However, such use in children is “off-label” as there is a paucity of methodologically sound controlled trials in children to inform optimal and safe dosing.

Prior pharmacological studies show that young children have up to 2-4 folds higher<sup>6</sup> clearance and volume of distribution of ketorolac compared to adolescents and adults. This suggests that younger children need a relatively higher dose per kilogram body weight than adults and the currently used 10-15 mg ceiling dose applied to adults<sup>7,8</sup> may not achieve equivalent analgesia in children. Emerging evidence, only applicable to adults, suggests that low-dose ketorolac (10 mg) is as effective as standard dose (30 mg) in acute pain management<sup>5,9-11</sup> with higher doses not conferring further benefit.<sup>12</sup> This has led to clinicians adopting the practice of a 10 mg maximum dose in children without rigorous pediatric evidence. For example, a 10 mg maximum dose in a 50 kg adolescent would equate to 0.2 mg/kg, in contrast to pediatric studies that used 0.5-1 mg/kg to a maximum of 20-30 mg.<sup>10,13-16</sup> In a recent survey (February 2022) our ED physicians, pediatric hospitalists and surgeons, 10/31 (32%) respondents said that they would administer ketorolac (0.5 mg/kg) up to a maximum of 30 mg, 20/31 (65%) use ketorolac up to a maximum of 10 mg and 1/31 (3%) did not know the best dose to give. Although the local monograph and order-sets recommend a maximum dose of 30 mg, our local variation in practice is not surprising and reflects clinical

uncertainty regarding the optimal dose.

Acutely painful conditions, when poorly treated, can result in delayed recovery, decreased patient satisfaction, chronic persistent post-surgical pain, hospital phobia and decreased trust in health care providers.<sup>17,18</sup> To our knowledge, there are no trials to guide selection of the most effective and safe ketorolac dose for use in children. This comes at a time when ketorolac is being considered more and more often to fill the non-opioid gap in treatment for moderate to severe pain.<sup>13,19-22</sup> Ketorolac is the only choice for IV analgesia that is non-opioid. Clinicians wish to decrease opioid use where possible.<sup>23</sup> However, recent evidence showed persistent opioid use among 4.8% of 88,637 post-operative pediatric patients compared to 0.1% in non-surgical patients.<sup>24</sup> Of major concern, opioid-related pediatric deaths increased by 268% between 1999-2016.<sup>25</sup> In response to the opioid crisis, the Canadian Institutes of Health Research have recognized it as a priority area for research and “teaching old drugs new tricks” is one of the prominent strategies.<sup>26</sup>

One of those “old drugs” is ketorolac tromethamine, an NSAID belonging to a group of non-opioid analgesics that inhibit the synthesis of prostaglandins and thromboxanes with strong analgesic and anti-inflammatory properties.<sup>4,27</sup> In Canada, ketorolac is available by IV administration and is indicated for moderate to severe pain.<sup>1-3</sup> As noted above, despite ketorolac’s widespread adaptation, its use in children is “off-label” as there is a paucity of methodologically sound trials for children to inform safe practice. Rigorous evidence for an effective, safe, non-opioid analgesic for children being evaluated in the ED could diminish the use of opioids while providing more effective, evidence-based treatment. Our national research network, Pediatric Emergency Research Canada (PERC) has a proud history of collaboration and success in pain trials.<sup>1,28,29</sup> With careful and deliberate collaboration, our team is poised to make a breakthrough in this area of research with a national impact.

We conducted and published<sup>30</sup> a systematic review and meta-analysis of 4 databases and trial registries in early 2022 to identify any RCTs regarding ketorolac dosing. There were no published pediatric trials. We identified four RCTs that included 392 adult participants. Studies compared standard dose ketorolac (30 mg) to either mid-dose ketorolac (15-20 mg) or low-dose ketorolac (10 mg). Most trials had small sample sizes and used a single dose of IV ketorolac,<sup>5,9,11</sup> with the exception of one study that used intramuscular ketorolac.<sup>31</sup> All trials used the 100-mm visual analogue scale (VAS) to measure their primary outcome pain level at 1 hour (3 trials)<sup>1,15,42</sup> or 4 hours (1 trial)<sup>11</sup> post-intervention. Four trials with 196 participants compared IV ketorolac 30 mg to 15-20 mg, with a non-significant mean difference of 1.03 mm (95% confidence interval [CI], [-2.45, 4.5]). Two trials with 116 participants compared ketorolac 30 mg to 10 mg and found a non-significant mean difference of 1.55 mm (95% CI [-2.42, 5.53]) favoring the 30 mg dose. There was consistency across all trials and an  $I^2$  of 0%. This suggests that, for adults with acute pain, there is no clinically or statistically meaningful difference between lower doses of ketorolac and standard doses, and that an analgesic ceiling to ketorolac is reached at 10 mg in adults.

Studying potentially effective non-opioid analgesics for moderate to severe pain in the era of the current opioid crisis is critically important to supporting judicious and responsible use of opioids. Ketorolac is an excellent alternative to opioids for moderate to severe pain and it is imperative to conduct pediatric dosing studies to inform both clinicians and regulatory agencies. Given the continued under-treatment of pain in children, its known adverse effects (including prolonged healing times, longer length of stay, less satisfaction)<sup>32</sup> and the lack of high quality evidence for ketorolac use in children, there is an urgent need for a well-designed, rigorously conducted trial to inform clinical treatment decisions and healthcare policy.



## **METHODS:**

### DESIGN:

Randomized, non-inferiority, double-dummy, double-blind, single-centre, mixed methods pediatric ED trial. The study will be conducted using recommendations from the 2010 CONSORT statement extension for noninferiority and equivalence trials.<sup>33</sup>

### OBJECTIVES AND HYPOTHESIS:

#### Primary Objective:

In children aged 6-17 years with moderate to severe pain (as measured on the 11-point verbal numerical rating scale (vNRS)) who are prescribed IV ketorolac by their treating physician, lower-dose IV ketorolac dosing strategies (0.25 mg/kg/dose up to 30 mg OR 0.5 mg/kg/dose up to 10 mg) are non-inferior (NI) to standard dosing (0.5 mg/kg/dose up to 30 mg) in reducing mean pain scores.

*Primary Hypothesis:* Low-dosing strategies will be non-inferior to standard dose by a margin of 1.0 on the 11-point vNRS: A) ketorolac given at 0.5 mg/kg/dose up to 10 mg will be non-inferior to standard dose ketorolac and B) ketorolac given at 0.25 mg/kg/dose up to 30 mg will be non-inferior to standard dose ketorolac.

*Secondary hypothesis:* 0.5 mg/kg/dose up to 10 mg will be superior to 0.25 mg/kg/dose up to 30 mg by the minimally important difference (MID) of 2.0 on the 11-point vNRS.

#### Secondary Objectives:

To understand patients' and caregivers' knowledge, attitudes, perceptions, and emotions on pain, medications, and their use in treating acute pain. As pain is a multi-dimensional experience, we seek a deeper understanding of participants' experiences with pain and pain medications by assessing the

following domains: 1) caregiver knowledge and attitudes towards widely available analgesics; 2) attitudes and fears associated with IV analgesics; and 3) caregiver perceptions of dosing of analgesics as well as AEs associated with them.

### INTERVENTIONS:

To maintain blinding of bedside clinical staff, patients, research staff, we will administer an active intervention (ketorolac) and two controls (identical normal saline placebo) to each patient at three differing doses.

i) Standard-dose group A:

**IV ketorolac 0.5 mg/kg to a maximum of 30 mg**

plus IV normal saline placebo given at 0.25 mg/kg to a maximum of 30 mg

plus IV normal saline placebo given at 0.5 mg/kg to a maximum of 10 mg

ii) Low-dose group B:

**Group B1: IV ketorolac 0.5 mg/kg to a maximum of 10 mg**

plus IV normal saline placebo given at 0.25 mg/kg to a maximum of 30 mg

plus IV normal saline placebo given at 0.5 mg/kg to a maximum of 30 mg

**Group B2: IV ketorolac 0.25 mg/kg to a maximum of 30 mg**

plus IV normal saline placebo given at 0.5 mg/kg to a maximum of 30 mg

plus IV normal saline placebo given at 0.5 mg/kg to a maximum of 10 mg

For rescue therapy, any participant can be given any other non-NSAID analgesic at the discretion of the treating MD at least 60 minutes after the trial medication is administered. To minimize

overdosing or AEs, any other NSAIDs can be given 6 hours post-intervention.

Rationale for Treatment Dose: Ketorolac is available at MCH (McMastre Chfor off-label use in children for moderate to severe pain. The acceptable dose range is 0.25-1 mg/kg/dose every 6 hours (maximum 30 mg/dose).<sup>34</sup> Onset of action is 30 minutes after IV administration and the maximum effect is achieved at 2 hours with a total duration of action up to 6 hours. Available population PK study data<sup>35</sup> from 3 studies on 64 children (intraoperative) showed a decrease in both central and peripheral volume of distribution over the first few years of life and clearance decreases from infancy to adolescence. A single dose of 0.5 mg/kg ketorolac (maximum dose 10-30 mg) every 6 hours achieved an EC<sub>50</sub> at or above the established of 0.37 mg/ml. Most of our participants aged 6 and above will weigh at least 20 kg (50<sup>th</sup> percentile) and receive the maximum ceiling dose of 10 mg (group B1). Hence, including low-dose group B2 (0.25 mg/kg to a maximum of 30 mg) will allow us to test two low dosing strategies since we are changing only 1 intervention/arm: 1) a lower dose per kg (0.25 mg/kg) is NI to standard dose (0.5 mg/kg) and 2) a lower ceiling dose (10 mg) is NI to standard ceiling dose (30 mg).

#### RANDOMIZATION AND PARTICIPANT ALLOCATION:

The study's research pharmacist at McMaster Children's Hospital (MCH) research pharmacy will create a simple computer-generated block randomization list using Robust Randomization App<sup>36</sup> with random varying permuted blocks of 3, 6 and 9 and a 1:1:1 allocation ratio. The research pharmacists will prepare consecutively numbered study drug vials according to the randomization schedule, with clear labels and dosing instructions in each kit. At least 3 study drug kits will be stored in the password protected ED medication dispensing machines as per standard operating procedures and Division 5 Good Clinical Practice Health Canada guidelines. Drug kits will be

replenished as needed (at minimum, weekly) by the research pharmacists. Only the research pharmacists will retain the randomization codes.

A log of all screened patients will be maintained. If patients are eligible, details of the study will be discussed with patients and their caregiver. Consent and assent will be obtained as per Hamilton integrated Research Ethics Board (HiREB) guidelines and approved consenting procedures. The CRA will collect baseline clinical variables and will complete the data collection forms. Elements of baseline pain severity (assessed by vNRS), type of pain, location of pain, duration of pain since onset, associated symptoms (e.g., nausea, anorexia, vomiting, dysuria, fever, pain with movement) will be collected. The CRA will then pick the next sequentially numbered drug kit and enter the drug kit coded number into REDCap. The research nurse will administer the study drugs to the patient (ketorolac and placebo normal saline) according to the dosing guidelines as an IV push over 5 minutes. Five minutes is a safe timeframe to administer IV ketorolac. This is consistent with the instructions on the clinical drug monograph at our hospital. Time 0 will be the time study drug administration is completed.

### **METHODS TO PROTECT FROM BIAS:**

Our study drug kits will contain active ketorolac and normal saline placebo (labelled as ketorolac) with instructions on dosing as per the randomization schedule (See section 2.2). Ketorolac is identical to normal saline placebo in appearance, consistency, and smell. Vials will contain clear liquid ketorolac 30 mg/ml or normal saline placebo ketorolac 30 mg/ml. Vials will be stored in consecutively numbered study drug kits according to the randomization schedule generated by the MCH research pharmacy. The double-dummy design will ensure blinding of the research nurse drawing up and administering the drug. MDs, RNs, participants, and their families, investigators,

research nurses and Clinical Research Assistants (CRAs) will all be masked to prevent bias in trial procedures and outcome assessment. Once participants are randomized, we will restrict all other pharmacologic analgesic co-interventions except acetaminophen and rescue therapy. Other medications that may be part of the patient's treatment plan such as antiemetics, antibiotics or antihistamines can be co-administered. Since our primary outcome is a self-reported pain scale, we will conduct the semi-structured survey after our outcomes are assessed. Research assistants can complete the semi-structured survey after the 6-hour outcome assessment or, if the patient is discharged, within 7 days by phone or electronically. The trial is registered on [www.clinicaltrials.gov](http://www.clinicaltrials.gov) (NCT05641363).

#### CONCOMITANT MEDICATIONS:

To decrease confounding effects of other analgesics, we will exclude anyone who prior to randomization, received any NSAIDs or opioids in the preceding 6 hours and 4 hours, respectively. We will not allow any other concomitant analgesics (except acetaminophen) administration during the study enrollment (from randomization to 60 minutes post-rescue therapy if it was required). Patients who have taken acetaminophen prior to randomization will be eligible to participate. Acetaminophen is widely available for use as an over-the-counter medication analgesic and is effective for mild pain but not for moderate or severe pain. Ketorolac should still be effective when given alongside acetaminophen and has a different mechanism of action. Additionally, in patients presenting with migraine, they will be allowed to have co-administration of anti-emetics such as metoclopramide or ondansetron. This should not affect our outcomes since all those patients will receive ketorolac (at differing doses) as the only analgesic. All co-interventions will be recorded.

#### SAMPLING STRATEGY:

Inclusion Criteria and justification:

1. Age 6.0 years to <18 years: primary outcome measure, 11-point vNRS is validated for use in children  $\geq 6$  years,<sup>37-39</sup> and no other evidence-based acute pain measure is recommended for use in younger children Currently experiencing moderate to severe pain (self-reported pain score  $>4$  using the vNRS at the time of enrollment; ketorolac is used to treat moderate to severe pain)<sup>40</sup>
2. Patients seen in the ED or inpatient setting with acute pain  $\leq 30$  days in duration<sup>5</sup>
3. Patient with IV cannula in situ or ordered (to minimize any additional pain or distress)

Exclusion criteria and justification:

1. Previous enrollment in trial (to ensure all observations are independent and not paired)
2. Post-operative patient (as this included medically induced pain, versus pathology-only)
3. NSAIDs 6 hours and/or opioids 4 hours prior to recruitment (avoid over-dosing and confounding).
4. Actively followed and treated by the chronic pain team (confounding as response to analgesics maybe altered).
5. Caregiver and/or child cognitive impairment (precludes the ability to respond to study questions)
6. History of gastrointestinal bleed or ulcers, inflammatory bowel disease, coagulation disorders, cerebrovascular bleeding, known arterio-vascular malformations (increased bleeding risk)
7. History of chronic and active renal disease, excluding renal calculi and urinary tract infections
8. History of chronic and active hepatocellular disease (ketorolac is metabolized in the liver)
9. Known pregnancy at the time of enrollment (risk of closure of patent ductus arteriosus in fetus)
10. Known hypersensitivity to NSAIDs or opioids
11. Inability to obtain consent (language barrier and the absence of language translator)

### DURATION OF TREATMENT AND FOLLOW-UP:

Ketorolac and placebo can be given as an IV slow push over 5 minutes with or without a drug pump. Only a single dose will be administered as part of the trial. The effects on pain will be monitored by obtaining baseline pain scores with the vNRS and at time 30, 60, 90, 120 minutes and at 6 hours if they are still in the hospital. At follow-up, ED and inpatient chart reviews will be completed to determine results of investigations, AEs, total doses of opioids administered in morphine-equivalents/kg, all types of NSAIDs administered and dose/frequency for each and the final diagnosis assigned. The survey will be completed within 7 to 14 days once all clinical outcomes are completed (6 hours post intervention).

### PRIMARY AND SECONDARY OUTCOME MEASURES:

#### A) PRIMARY OBJECTIVE:

##### i) Primary endpoint:

Between each low-dose ketorolac group (B1 and B2) and standard group (A) mean differences in pain as measured on vNRS at 60 minutes. We selected 60 minutes post-administration as the time of our primary outcome assessment after careful consideration and in discussion with our parent/youth collaborators and our clinical pharmacologist co-investigator. This time point 1) allows children to settle from anxiety associated with IV start, which may confound pain assessment; 2) is an acceptable time point for fair assessment of the analgesic effects of the study drug, with a good balance between onset and peak effect for ketorolac; and 3) is a reasonable timeframe for patients to expect relief from moderate to severe pain.

ii) Secondary endpoints:

1. vNRS score at 30, 90 and 120 minutes as well as 6 hours post administration.
2. Proportion of participants who achieves the 2-point vNRS MID pain score reduction at 60 and 120 minutes
3. Proportion of participants who change the severity of their baseline pain category at all time points (mild = 0 to 3, moderate = 4 to 6, severe  $\geq 7$  on the vNRS)<sup>38</sup>
4. Time to effective analgesia (i.e., time at which a vNRS  $< 3$  is achieved post-intervention)
5. Proportion of participants requiring any rescue analgesia in each trial arm
6. Total amount administered as measured by morphine equivalent mg/kg within 8 hours of intervention

iii) Safety outcomes:

1. The proportion of children experiencing any adverse events (AEs), as reported by caregivers or clinical staff, will be recorded in accordance with the CONSORT Harms checklist.<sup>41</sup> We will solicit specific expected AEs that we found from our SR<sup>42</sup> to be commonly reported with NSAIDs such as gastric pain. Additionally, we will have open-ended questions to collect information on any additional unexpected AEs.
2. Frequency of each specific AE (e.g., nausea, vomiting). Time frame is 8 hours post drug administration

**B) Secondary Objective:**

Semi-structured survey with baseline demographics, closed-ended questions (7-point Likert scale) and open-ended interview questions will be collated, summarized, and analyzed by sub-group (age, gender). Time frame for completion is 7 to 14 days post randomization.

### OUTCOME MEASUREMENT TOOLS:

We will measure pain using the 11-point vNRS, a validated self-reported acute pain scale for which an anchor-based MID has been established (2 points). The vNRS has demonstrated strong convergent validity, known-groups validity, responsiveness, and test-retest reliability in children 6 to 17 years old with acute pain and in the emergency setting.<sup>38,39</sup> It is rapidly administered by asking “On a scale of 0 to 10, where 0 means no pain and 10 means the worst pain, how much pain do you have right now?” In a recent systematic review of all acute pain scales for children, the vNRS was the only one to receive a strong recommendation for use in children  $\geq 6$  years in age.<sup>37</sup> A phone or electronic questionnaire will be administered after all pain assessments are completed within 7-days to 14-days of enrollment, either in person or by phone or email to assess 1) caregiver knowledge and attitudes towards widely available analgesics; 2) attitudes and fears associated with IV analgesics; and 3) caregiver perceptions of dosing of analgesics as well as AEs associated with them.

### SAMPLE SIZE CALCULATIONS:

Based on adult studies,<sup>5,9,11,31</sup> we estimated a standard deviation of 1.5 in each group and a mean difference of 0.2. The NI margin of 1.0 is carefully selected to ensure that a rejection of the null hypothesis would: (1) include the effect size that standard dose ketorolac has historically displayed when compared to placebo (relative risk of achieving 50% pain reduction compared to placebo 2.81, 95% confidence interval (CI) [1.8-4.4] with number needed to treat of 2.4, 95% CI [1.8, 3.7]),<sup>10</sup> and (2) exclude clinically important levels of inferiority by keeping our margin at 50% of the known MID of 2.0 on the vNRS, ensuring ethical and relevant clinical application. A statistician (JE) using nQuery Software, calculated a total sample size of 171 participants (57/group), which would allow us to test our NI hypothesis using a one-sided alpha of 0.025, 80% power and a NI margin ( $\Delta$ ) of 1.0.

Since our primary outcome is short-term (60 minutes) and we are testing a single dose of ketorolac, we expect very few patients withdraws or loss to follow-up, but we will increase our sample size by 5%, to 60/group to account for any unanticipated withdrawals.

### ANALYSIS PLAN:

A) Primary objective analysis plan: Data will be described in terms of mean (SD) or 95% confidence limits for normally distributed data and frequency (percentage) in the case of categorical data. Primary endpoint is the difference between the mean reduction in pain scores between each of the low-dose groups (B1, B2) and the standard dose group (A) 60 minutes post intervention. The primary analysis will include all subjects randomized based on the intention to treat analysis and a sensitivity per-protocol analysis will also be performed. *A-priori*, the primary analysis will be adjusted for baseline pain scores using the analysis of covariance (ANCOVA). Generalized Estimating Equations will be used to examine the impact of baseline pain score covariate longitudinally across the entire time frame on pain as measured by vNRS. *NI would be shown if the lower limit of the 95% CI for the between group (groups B1 to A or B2 to A) differences in the primary endpoint in cm is >1.0.* If >5%<sup>43</sup> of our vNRS scores are missing within 120 minutes, we will employ multiple imputation to create 5 data sets wherein any missing pain datum will be imputed with the Markov chain Monte Carlo method. For secondary endpoints, we will describe those outcomes using descriptive statistics and perform a linear (continuous), logistic or ordinal regression (categorical or ordinal). If both low-dose strategies are shown to be NI to standard dose, we will conduct an exploratory analysis to see if one low-dosing strategy is superior to the other (*group B1 vs B2*). This will be conducted using ANCOVA to adjust for baseline pain scores and superiority will be determined by a difference that is defined by the MID of 2.0 on the 11-point vNRS. All analyses will be done using (SAS Proc MI; SAS 9.4; SAS Inc, Cary, NC).

Adverse Event Profile Analysis: The proportion of children experiencing any AEs as reported by

caregivers, MDs or RNs will be compared between groups using logistic regression and presented with their corresponding binomial 95% two-sided CI. The analysis will evaluate the presence/absence of AEs in each group such as nausea, epigastric pain, or dyspepsia.

#### B) Secondary objective analysis plan:

i) Summative statistics will be used to describe distribution of responses to closed-ended questions. Answers to open-ended questions will be thematically coded; concepts and themes will be developed using a constant comparative method of analysis. Themes related to knowledge of pain and analgesia, fears of AEs or effectiveness of analgesia, satisfaction or dissatisfaction with current therapy will be categorized, among others.

#### **FREQUENCY OF ANALYSIS:**

The Data Safety Monitoring Board (DSMB) will be provided with a masked comparison between treatment groups with respect to the adverse events at the intervals of their choosing. We will inform the DSMB of all serious adverse events (SAE) within 7-days of their occurrence. At the DSMB's request, they can receive the associated p-values. They can further request unmasking. The DSMB board will be completely independent from the trial steering committee and will have a clinical ED physician, a clinical researcher and a biostatistician who are not associated with trial sponsor, principal investigator or had any input on study methodology.

#### **PLANNED SUBGROUPS:**

a) Headaches and acute abdominal pain, the two most common indications for IV ketorolac, no subgroup effect is anticipated given evidence that cause of pain does not alter response to analgesia:<sup>44,45</sup>

- b) Age  $\geq 12$ , adolescents' drug metabolism differ from younger age groups;
- c) Gender (grouped as cisgender, transgender and other); and
- d) Sex (male, female and intersex). Biological mechanisms, such as sex hormones, influence the nervous system's perception of pain and response to analgesics).<sup>46-48</sup> In addition, gender norms are known to impact a patient's perceived sensitivity to pain. We will advise participants and caregivers why sex and gender are important in pain research and then use the recommended<sup>49</sup> 2-step questionnaire to determine biological sex and gender separately. The 2-step survey has been tested in transgender populations and validated over a broader North American population;<sup>50-54</sup>
- e) Race and ethnicity: We will collect race and ethnicity data using the standard Canadian Institute for Health Information data questionnaire, with two questions on Indigenous identity data standard and race-based data standard.<sup>55</sup> We will use this data to help design further subgroup analyses.

#### TRIAL DAY TO DAY OPERATIONS:

A study coordinator with experience in Health Canada drug trials will work with PI (ME, LG). CRAs and research nurses will be available to recruit at MCH from 8 am-9 pm. We will present the study to staff physicians in the Pediatric Emergency Department, General Pediatrics and Pediatric Surgery so they are aware of the study eligibility criteria and how to contact the study team members. Our research nurse will perform daily rounds in the ED and on the wards during clinical rounds to ask and remind the clinical team of any potential participants. The clinical team will obtain ask potential participants if they would like to be approached by research personnel since they may be eligible for KETO DOSE trial. If patient agrees, they will be approached by research staff to check eligibility. If eligible, details of the study will be discussed with patient and caregiver. Children and caregivers will be consented and assented for participation in the KETODOSE pain trial, including the follow-up survey. Once caregivers' consent and participants assent, the research nurse will obtain the drug kit from the ED drug dispensing machine and assign them the drug kit with the smallest subsequent

number. Data will be prospectively collected on baseline characteristics including age, sex, gender, baseline pain severity (vNRS), type of pain, location and duration of pain and associated symptoms. Following randomization, the study drug kit containing the study drug vials and information for dosing will be administered to the patient by the research nurse or bedside nurse with CRA assistance. Time 0 (baseline) will be considered the time study drug administration has been completed. Patients will be followed for the hospital duration and a chart review will be completed. Medical records will be checked a week after the index visit for return visits to the ED and reasons for return visit.

#### SAFETY OVERSIGHT:

Safety oversight will be under the direction of a DSMB composed of individuals with the appropriate expertise, including trial methodology, epidemiology & biostatistics, and a pediatrician or a pediatric surgeon. Members of the DSMB will be independent from the study conduct and free of conflict of interest, or measures should be in place to minimize perceived conflict of interest. The DSMB will meet at least semiannually to assess safety and efficacy data for both trials in this study. The DSMB will operate under the rules of an approved charter/terms of reference that will be reviewed at the organizational meeting of the DSMB. At this time, each data element that the DSMB needs to assess will be defined. The DSMB will provide its input to the PI and the Study coordinator. The DSMB may also provide input to the HiREB and Health Canada if requested.

**DISCUSSION:**

Optimal dosing of ketorolac for acute pain management in children remains uncertain. Although intravenous ketorolac is widely used in pediatric emergency settings, current dosing strategies are largely extrapolated from adult studies or based on clinical opinion rather than pediatric-specific evidence. Pharmacokinetic differences between children and adults, such as increased clearance and volume of distribution in younger children, further challenge the application of adult dosing regimens in pediatric populations. Additionally, although emerging adult data suggest an analgesic ceiling effect at 10 mg of ketorolac, no pediatric trials have rigorously evaluated this hypothesis, leading to substantial practice variation and clinical uncertainty.

The KETODOSE trial is designed to address this critical evidence gap by comparing two lower-dose IV ketorolac strategies to the standard dosing regimen in children aged 6 to 17 years with moderate to severe pain. By using a randomized, double-dummy, double-blind, non-inferiority design aligned with CONSORT guidelines, the study aims to generate high-quality evidence that is directly applicable to pediatric emergency care. In parallel, the inclusion of a mixed-methods evaluation of caregiver knowledge, attitudes, and perceptions recognizes the multidimensional nature of pain management and the importance of family-centered care.

If the trial demonstrates that lower doses are non-inferior to standard dosing, the results may facilitate safer prescribing practices, reduce drug-related adverse events, and support broader efforts to minimize opioid use in children—a particularly pressing need in the context of the ongoing opioid crisis. The findings would also directly inform dosing guidelines, institutional order sets, and educational initiatives aimed at standardizing evidence-based non-opioid analgesia for pediatric acute pain.

Despite its strengths—including rigorous methodology, clinically meaningful outcomes, and a strong

KT strategy—the study’s single-center design may limit external generalizability. However, by building a robust infrastructure and engaging national partners, the KETODOSE trial is positioned to serve as a foundation for future multi-center investigations into pediatric non-opioid pain management.

Upon completion, this trial will provide urgently needed evidence to inform the optimal dosing of ketorolac in children, helping to advance safe, effective, and standardized acute pain care across pediatric emergency departments.

**Table 1: Summary of Outcomes and Analysis**

| OBJECTIVES                                                                                                                                                    | OUTCOME MEASURE                                                                                                                                                               | HYPOTHESIS                                                                                                                                                                                                                                                                                                                                                        | ANALYSIS                                                                     |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------|
| <b>PRIMARY EFFICACY OUTCOME*</b>                                                                                                                              |                                                                                                                                                                               |                                                                                                                                                                                                                                                                                                                                                                   |                                                                              |
| Pain relief: To determine if low-dose intravenous (IV) ketorolac regimens are non-inferior to standard dose IV ketorolac in relieving moderate to severe pain | Primary efficacy endpoint: Pain level as reported by participants on an 11-point verbal numerical rating scale (vNRS) score at 60 minutes post administration of trial drugs. | A) ketorolac given at 0.5 mg/kg/dose up to 10 mg will be non-inferior to standard dose ketorolac and B) ketorolac given at 0.25 mg/kg/dose up to 30 mg will be non-inferior to standard dose ketorolac.<br>B) 0.5 mg/kg/dose up to 10 mg will be superior to 0.25 mg/kg/dose up to 30 mg by the minimally important difference (MID) of 2.0 on the 11-point vNRS. | -Intention to treat analysis using ANCOVA: adjusted for baseline pain scores |
| <b>SAFETY OUTCOME</b>                                                                                                                                         |                                                                                                                                                                               |                                                                                                                                                                                                                                                                                                                                                                   |                                                                              |
| To determine between group differences in proportion with adverse events (AEs)                                                                                | Safety endpoint: The proportion of children experiencing AEs related to study drug administration                                                                             | Participants who receive low-dose IV ketorolac regimen will have fewer AEs than participants who receive standard dose IV ketorolac                                                                                                                                                                                                                               | Regression analysis                                                          |
| <b>SECONDARY OUTCOMES</b>                                                                                                                                     |                                                                                                                                                                               |                                                                                                                                                                                                                                                                                                                                                                   |                                                                              |
| <b>i) EFFICACY</b>                                                                                                                                            |                                                                                                                                                                               |                                                                                                                                                                                                                                                                                                                                                                   |                                                                              |
| Pain relief at all time points                                                                                                                                | Between group differences in pain score at all study time points at 30, 90, 120 minutes and at 6-8 hours post administration of trial drugs.                                  | Low dose regimens will be non-inferior to standard dose at all time points.                                                                                                                                                                                                                                                                                       | Generalized Estimating Equations: Adjusted for baseline pain scores          |
| Pain relief by the minimal important difference (MID)                                                                                                         | Proportion who achieves a 2-point vNRS (MID) pain score reduction at 60 and 120 minutes                                                                                       | Low dose ketorolac will be non-inferior to standard dose ketorolac regimens in reducing pain by the 2-point MID on vNRS                                                                                                                                                                                                                                           | Regression analysis                                                          |
| Pain category change                                                                                                                                          | Proportion of participants who change their baseline pain category at all time points (mild 1 to 3, moderate 4 to 6, severe $\geq 7$ on vNRS)                                 | No difference between low dose and standard dose ketorolac in pain category change at all time points                                                                                                                                                                                                                                                             | Regression analysis                                                          |
| Time to achieve mild or no pain level                                                                                                                         | Time to effective analgesia as measured by the time when vNRS of $<3$ is achieved                                                                                             | No difference between all ketorolac dosing arms.                                                                                                                                                                                                                                                                                                                  | Cox regression analysis                                                      |
| Rescue analgesia                                                                                                                                              | Proportion of participants requiring any additional analgesia in each trial arm                                                                                               | There will be no difference between all ketorolac dosing arms                                                                                                                                                                                                                                                                                                     | Regression analysis                                                          |
| Opioid sparing                                                                                                                                                | Total amount of opioid administered as measured by morphine equivalent mg/kg within 8 hours of intervention                                                                   | There will be no difference between all ketorolac dosing arms                                                                                                                                                                                                                                                                                                     | Regression analysis                                                          |
| <b>ii) SAFETY</b>                                                                                                                                             |                                                                                                                                                                               |                                                                                                                                                                                                                                                                                                                                                                   |                                                                              |
| Adverse events frequency                                                                                                                                      | Frequency of each specific AE related to study drug administration (e.g., nausea, dizziness, drowsiness, gastric pain, headache, pruritis, constipation)                      | There will be more AEs associated with standard dose ketorolac compared to low dose regimens                                                                                                                                                                                                                                                                      | Regression analysis                                                          |
| <b>SUBGROUPS</b>                                                                                                                                              |                                                                                                                                                                               |                                                                                                                                                                                                                                                                                                                                                                   |                                                                              |
| Underlying condition                                                                                                                                          | Proportion of patients with headaches and acute abdominal pain, the two most common indications for IV ketorolac                                                              | no subgroup effect is anticipated given evidence that cause of pain does not alter response to analgesia <sup>44,45</sup>                                                                                                                                                                                                                                         | Regression analysis                                                          |
| Sex assigned at birth                                                                                                                                         | Proportion of male, female, and intersex                                                                                                                                      | Female sex will have stronger response to analgesia                                                                                                                                                                                                                                                                                                               | Regression analysis                                                          |
| Gender                                                                                                                                                        | Proportions of boy/man, girl/woman, transgender, non-binary, gender queer, gender fluid, two-spirit, other (as defined by participant)                                        | Differential treatment effect for girl/woman compared to boy/man gender.                                                                                                                                                                                                                                                                                          | Regression analysis                                                          |
| Age                                                                                                                                                           | Dichotomized to 6 to 11 years vs. 12-17 years, since developmental and hormonal changes might impact response to analgesia                                                    | Differential treatment effect based on age                                                                                                                                                                                                                                                                                                                        | Regression analysis                                                          |
| Race and ethnicity                                                                                                                                            | Proportion of participants in each indigenous and race category as per Canadian Institute for Health Information data questionnaire                                           | Differential treatment effect based on race (analysis depended on frequency and diversity of responses)                                                                                                                                                                                                                                                           | Regression analysis                                                          |

| SENSITIVITY ANALYSIS  |                                                                                                                                                                                                                                                                                        |                                                                    |                                                                      |
|-----------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------|----------------------------------------------------------------------|
| Per protocol analysis | Primary outcome: pain level as reported by participants on vNRS score at 60 minutes post-administration of trial drugs.<br>Safety outcome: Proportion of children experiencing AEs related to study drug administration, as reported by caregivers or clinical staff will be recorded. | The primary intention to treat analysis results will remain robust | ANCOVA: adjusted for baseline pain scores<br><br>Regression analysis |

\*Sample size calculation is based on primary efficacy outcome.

Abbreviations: AEs=Adverse Events, vNRS=11-point verbal Numerical Rating Scale, MID=Minimal Important Difference, IV=intravenous, RSS=Ramsay sedation score

1. Poonai N, Bhullar G, Lin K, et al. Oral administration of morphine versus ibuprofen to manage postfracture pain in children: a randomized trial. *CMAJ*. 2014;186(18):1358-1363.
2. Poonai N, Dattoo N, Ali S, et al. Oral morphine versus ibuprofen administered at home for postoperative orthopedic pain in children: a randomized controlled trial. *CMAJ*. 2017;189(40):E1252-E1258.
3. Krauss BS, Calligaris L, Green SM, Barbi E. Current concepts in management of pain in children in the emergency department. *Lancet*. 2016;387(10013):83-92.
4. Gillis JC, Brogden RN. Ketorolac. A reappraisal of its pharmacodynamic and pharmacokinetic properties and therapeutic use in pain management. *Drugs*. 1997;53(1):139-188.
5. Motov S, Yasavolian M, Likourezos A, et al. Comparison of Intravenous Ketorolac at Three Single-Dose Regimens for Treating Acute Pain in the Emergency Department: A Randomized Controlled Trial. *Ann Emerg Med*. 2017;70(2):177-184.
6. Brocks DR, Jamali F. Clinical pharmacokinetics of ketorolac tromethamine. *Clin Pharmacokinet*. 1992;23(6):415-427.
7. Lyon C, Claus LW. Less is more when it comes to ketorolac for pain. *J Fam Pract*. 2019;68(1):41-42.
8. Shrikant Kulkarni N. No Added Benefit with Higher Doses of Ketorolac for Treatment of Acute Pain in the Emergency Department. *Am Fam Physician*. 2017;96(4):262.
9. Eidinejad L, Bahreini M, Ahmadi A, Yazdchi M, Thiruganasambandamoorthy V, Mirfazaelian H. Comparison of intravenous ketorolac at three doses for treating renal colic in the emergency department: A noninferiority randomized controlled trial. *Acad Emerg Med*. 2021;28(7):768-775.
10. McNicol ED, Rowe E, Cooper TE. Ketorolac for postoperative pain in children. *Cochrane Database Syst Rev*. 2018;7:CD012294.
11. Duttchen KM, Lo A, Walker A, et al. Intraoperative ketorolac dose of 15mg versus the standard 30mg on early postoperative pain after spine surgery: A randomized, blinded, non-inferiority trial. *J Clin Anesth*. 2017;41:11-15.
12. Anderson BJ, Lerman J, Coté CJ. 7 - Pharmacokinetics and Pharmacology of Drugs Used in Children. In: Coté CJ, Lerman J, Anderson BJ, eds. *A Practice of Anesthesia for Infants and Children (Sixth Edition)*. Philadelphia: Elsevier; 2019:100-176.e145.
13. Neri E, Maestro A, Minen F, et al. Sublingual ketorolac versus sublingual tramadol for moderate to severe post-traumatic bone pain in children: a double-blind, randomised, controlled trial. *Arch Dis Child*. 2013;98(9):721-724.
14. Beiter JL, Jr., Simon HK, Chambliss CR, Adamkiewicz T, Sullivan K. Intravenous ketorolac in the emergency department management of sickle cell pain and predictors of its effectiveness. *Arch Pediatr Adolesc Med*. 2001;155(4):496-500.
15. Morteza Talebi Doluee BRK, Hamid Heidarian Mir, Mahsa Fateminayyeri, Farideh Madanitorbati and Somayyehalsadat Hosseini. Pain Relief in the Sickle-Cell Crisis: Intravenous Morphine Versus Ketorolac; A Double-Blind, Randomized Clinical Trial. *Iran Red Crescent Med J*. 2019;21(4).
16. Pierce MC, Fuchs S. Evaluation of ketorolac in children with forearm fractures. *Acad Emerg Med*. 1997;4(1):22-26.

17. Gan TJ. Poorly controlled postoperative pain: prevalence, consequences, and prevention. *J Pain Res.* 2017;10:2287-2298.
18. Baratta JL, Schwenk ES, Viscusi ER. Clinical consequences of inadequate pain relief: barriers to optimal pain management. *Plast Reconstr Surg.* 2014;134(4 Suppl 2):15S-21S.
19. Brown CR, Moodie JE, Dickie G, et al. Analgesic efficacy and safety of single-dose oral and intramuscular ketorolac tromethamine for postoperative pain. *Pharmacotherapy.* 1990;10(6 ( Pt 2)):59S-70S.
20. Catapano MS. The analgesic efficacy of ketorolac for acute pain. *J Emerg Med.* 1996;14(1):67-75.
21. Fricke JR, Jr., Angelocci D, Fox K, McHugh D, Bynum L, Yee JP. Comparison of the efficacy and safety of ketorolac and meperidine in the relief of dental pain. *J Clin Pharmacol.* 1992;32(4):376-384.
22. Adams AJ, Buczek MJ, Flynn JM, Shah AS. Perioperative Ketorolac for Supracondylar Humerus Fracture in Children Decreases Postoperative Pain, Opioid Usage, Hospitalization Cost, and Length of Stay. *J Pediatr Orthop.* 2019.
23. Fowler M, Ali S, Gouin S, et al. Knowledge, attitudes and practices of Canadian pediatric emergency physicians regarding short-term opioid use: a descriptive, cross-sectional survey. *CMAJ Open.* 2020;8(1):E148-E155.
24. Harbaugh CM, Lee JS, Hu HM, et al. Persistent Opioid Use Among Pediatric Patients After Surgery. *Pediatrics.* 2018;141(1).
25. Gaither JR, Shabanova V, Leventhal JM. US National Trends in Pediatric Deaths From Prescription and Illicit Opioids, 1999-2016. *JAMA Netw Open.* 2018;1(8):e186558.
26. Canadian Pain Research Summit Report (2016) - CIHR. <https://irsc-cihr.gc.ca/e/50558.html>. Published 2017. Updated 2017-09-29. Accessed.
27. Reinhart DI. Minimising the adverse effects of ketorolac. *Drug Saf.* 2000;22(6):487-497.
28. Poonai N, Kumar K, Coriolano K, et al. Hyoscine butylbromide versus acetaminophen for nonspecific colicky abdominal pain in children: a randomized controlled trial. *CMAJ.* 2020;192(48):E1612-E1619.
29. Ali S, Rajagopal M, Klassen T, et al. Study protocol for two complementary trials of non-steroidal or opioid analgesia use for children aged 6 to 17 years with musculoskeletal injuries (the No OUCH study). *BMJ Open.* 2020;10(6):e035177.
30. Forestell B, Sabbineni M, Sharif S, Chao J, Eltorki M. Comparative Effectiveness of Ketorolac Dosing Strategies for Emergency Department Patients With Acute Pain. *Ann Emerg Med.* 2023;82(5):615-623.
31. Turner NJ, Long DA, Bongiorno JR, et al. Comparing two doses of intramuscular ketorolac for treatment of acute musculoskeletal pain in a military emergency department. *Am J Emerg Med.* 2021;50:142-147.
32. Lynch ME. The need for a Canadian pain strategy. In: *Pain Res Manag.* Vol 16.2011:77-80.
33. Piaggio G, Elbourne DR, Pocock SJ, Evans SJ, Altman DG, Group C. Reporting of noninferiority and equivalence randomized trials: extension of the CONSORT 2010 statement. *JAMA.* 2012;308(24):2594-2604.
34. Forrest JB, Heitlinger EL, Revell S. Ketorolac for postoperative pain management in children. *Drug Saf.* 1997;16(5):309-329.
35. McLay JS, Engelhardt T, Mohammed BS, et al. The pharmacokinetics of intravenous ketorolac in children aged 2 months to 16 years: A population analysis. *Paediatr Anaesth.* 2018;28(2):80-86.
36. APPS CR. RRAp Robust Randomization App (Version 3.1.1) [Website application software].

- <http://clinicalresearch-apps.com/RRApp.html>. Published 2017. Accessed 2020.
37. Birnie KA, Hundert AS, Lalloo C, Nguyen C, Stinson JN. Recommendations for selection of self-report pain intensity measures in children and adolescents: a systematic review and quality assessment of measurement properties. *Pain*. 2019;160(1):5-18.
  38. Tsze DS, Hirschfeld G, von Baeyer CL, Suarez LE, Dayan PS. Changes in Pain Score Associated With Clinically Meaningful Outcomes in Children With Acute Pain. *Acad Emerg Med*. 2019;26(9):1002-1013.
  39. Tsze DS, von Baeyer CL, Pahalyants V, Dayan PS. Validity and Reliability of the Verbal Numerical Rating Scale for Children Aged 4 to 17 Years With Acute Pain. *Ann Emerg Med*. 2018;71(6):691-702 e693.
  40. Canada P. Ketorolac Tromethamine Injection Product\_Monograph\_209949.pdf. [https://www.pfizer.ca/sites/default/files/201712/2017.12.01\\_Ketorolac\\_PM\\_E\\_209949.pdf](https://www.pfizer.ca/sites/default/files/201712/2017.12.01_Ketorolac_PM_E_209949.pdf). Published 2017. Accessed 2021/01/07, 2021.
  41. Ioannidis JP, Evans SJ, Gotzsche PC, et al. Better reporting of harms in randomized trials: an extension of the CONSORT statement. *Ann Intern Med*. 2004;141(10):781-788.
  42. Hartling L, Ali S, Dryden DM, et al. How Safe Are Common Analgesics for the Treatment of Acute Pain for Children? A Systematic Review. *Pain Res Manag*. 2016;2016:5346819.
  43. Jakobsen JC, Gluud C, Wetterslev J, Winkel P. When and how should multiple imputation be used for handling missing data in randomised clinical trials - a practical guide with flowcharts. *BMC Med Res Methodol*. 2017;17(1):162.
  44. Busse JW, Sadeghirad B, Oparin Y, et al. Management of Acute Pain From Non-Low Back, Musculoskeletal Injuries : A Systematic Review and Network Meta-analysis of Randomized Trials. *Ann Intern Med*. 2020;173(9):730-738.
  45. Busse JW, Wang L, Kamaleldin M, et al. Opioids for Chronic Noncancer Pain: A Systematic Review and Meta-analysis. *JAMA*. 2018;320(23):2448-2460.
  46. Robinson ME, Riley JL, 3rd, Myers CD, et al. Gender role expectations of pain: relationship to sex differences in pain. *J Pain*. 2001;2(5):251-257.
  47. Wise EA, Price DD, Myers CD, Heft MW, Robinson ME. Gender role expectations of pain: relationship to experimental pain perception. *Pain*. 2002;96(3):335-342.
  48. Alabas OA, Tashani OA, Tabasam G, Johnson MI. Gender role affects experimental pain responses: a systematic review with meta-analysis. *Eur J Pain*. 2012;16(9):1211-1223.
  49. Gendered Innovations in Science and Medicine, Engineering and Environment- Surveys. Stanford. <http://genderedinnovations.stanford.edu/methods/surveys.html>. Published 2021. Accessed 2021/2/2, 2021.
  50. Deutsch MB, Green J, Keatley J, et al. Electronic medical records and the transgender patient: recommendations from the World Professional Association for Transgender Health EMR Working Group. *J Am Med Inform Assoc*. 2013;20(4):700-703.
  51. Factor R, & Rothblum, E. Exploring gender identity and community among three groups of transgender individuals in the United States: MTFs, FTMs, and genderqueers. *Health Sociology Review*. 2008;17(3):235-253.
  52. Group G. Best practices for asking questions to identify transgender and other gender minority respondents on population-based surveys. *Los Angeles: Williams Institute*. 2014.
  53. Jans M, Grant, D., Park, R., Kil, J., Viana, J., Lordi, N., Herman, J. L. Using verbal paradata monitoring and behavior coding to pilot test gender identity questions in the California Health Interview Survey: the role of qualitative and quantitative feedback. Paper presented at: In Proceedings of the American Association for Public Opinion Research Annual Conference. 2015.

54. Cahill S, Singal R, Grasso C, et al. Do ask, do tell: high levels of acceptability by patients of routine collection of sexual orientation and gender identity data in four diverse American community health centers. *PLoS One*. 2014;9(9):e107104.
55. Information ClfH. Guidance on the Use of Standards for Race-Based and Indigenous Identity Data Collection and Health Reporting in Canada. Ottawa. CIHI. <https://www.cihi.ca/sites/default/files/document/guidance-and-standards-for-race-based-and-indigenous-identity-data-en.pdf>. Published 2022. Accessed 2022 Aug 29, 2022.



## Supplementary Files

## Multimedia Appendixes

Grant peer review.

URL: <http://asset.jmir.pub/assets/ac122d07b9f4ea4e59ccf8aeef4cdb92.pdf>