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Intravenous ketorolac versus morphine in children presenting with suspected appendicitis: a pilot single-centre non-inferiority randomised controlled trial

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ABSTRACT

Objectives Despite a lack of evidence demonstrating superiority to non-steroidal anti-inflammatory drugs, like ketorolac, that are associated with lower risk of harms, opioids remain the most prescribed analgesic for acute abdominal pain. In this pilot trial, we will assess the feasibility of a definitive trial comparing ketorolac with morphine in children with suspected appendicitis. We hypothesise that our study will be feasible based on a 40% consent rate.

Methods and analysis A single-centre, non-inferiority, blinded (participant, clinician, investigators and outcome assessors), double-dummy randomised controlled trial of children aged 6–17 years presenting to a paediatric emergency department with ≤5 days of moderate to severe abdominal pain (≥5 on a Verbal Numerical Rating Scale) and are investigated for appendicitis. We will use variable randomised blocks of 4–6 and allocate participants in 1:1 ratio to receive either intravenous (IV) ketorolac 0.5 mg/kg+IV morphine placebo or IV morphine 0.1 mg/kg+IV ketorolac placebo. Analgesic co-intervention will be limited to acetaminophen (commonly used as first-line therapy). Participants in both groups will be allowed rescue therapy (morphine 0.5 mg/kg) within 60 min of our intervention. Our primary feasibility outcome is the proportion of eligible patients approached who provide informed consent and are enrolled in our trial. Our threshold for feasibility will be to achieve a ≥40% consent rate, and we will enrol 100 participants into our pilot trial.

Ethics and dissemination Our study has received full approval by the Hamilton integrated Research Ethics Board. We will disseminate our study findings at national and international paediatric research conferences to garner interest and engage sites for a future multicentre definitive trial.

Trial registration NCT04528563, Pre-results.

Strengths and limitations of this study

- Ketorolac is a promising well-established non-steroidal anti-inflammatory drug that has a better short-term side effect profile versus opioids and is not known as a substance of misuse.
- Our pilot study will inform the feasibility of conducting a large parallel-group, double-dummy, non-inferiority randomised controlled trial comparing ketorolac with morphine for moderate to severe acute abdominal pain in children.
- Patient-centred design with robust validated outcomes.
- Double-dummy design ensures blinding of patients and clinicians and reduces bias in outcome reporting.
- Limitations include exclusion of very young patients and short-term follow-up.

BACKGROUND

Acute appendicitis is a common clinical condition resulting from inflammation and infection of the appendix. In Canada, appendicitis is the most common reason for emergency surgical intervention among children aged 6–17 years, and the second most common reason for hospitalisation, accounting for 8000 admissions annually in this age group.[1] Despite this, appendicitis can be challenging to diagnose, investigations are time-consuming (4–6 hours),[2 3] and children experience considerable pain secondary to infection, inflammation, localised or generalised peritonitis and tenderness exacerbated by multiple abdominal clinical assessments.[4–6]

Opioids remain the most prescribed analgesic by many specialties, including surgeons and emergency physicians, despite the ongoing opioid crisis.[7–10] Prior work by our team has demonstrated the non-superiority of opioids to non-opioid analgesics to treat moderately painful conditions, such as paediatric fractures.[11] As for the initial analgesic use in the emergency department (ED), there is no evidence that opioids provide clinically important improvements in pain scores when compared with

non-steroidal anti-inflammatory drugs (NSAIDs) for many conditions.[11–16]

There is significant practice pattern variation related to the choice of analgesics for patients with suspected appendicitis across Canada's 13 paediatric EDs.[17] The between-site range of the frequency of providing any analgesia to children with appendicitis is 36%–82%, in which 45%–90% were opioid analgesics. This variability stems, in part, from a paucity of appendicitis pain trials[18 19] coupled with concerns over contributing to the opioid crisis, which has led to young Canadians aged 15–24 years experiencing the highest reported morbidity from opioid overdoses, relative to other ages.[7] Consequently, clinicians are looking to responsibly decrease opioid use, where possible,[20] but also ensure optimal pain management. Recent evidence shows persistent opioid use 90–180 days after a surgical procedure among 4.8% of 88 637 postoperative paediatric patients compared with 0.1% in non-surgical patients.[10] In addition, between 1999 and 2016, opioid-related paediatric deaths in the USA increased by 268%.[9] The Canadian Institute of Health Research has recognised optimising use of opioid analgesia as a priority area for research[21] and 'teaching old drugs new tricks' as an important strategy[22] to explore opportunities for opioid substitution.

One of those 'old drugs', ketorolac tromethamine, is an NSAID that belongs to a group of non-opioid analgesics that inhibit the synthesis of prostaglandins and thromboxanes. In Canada, ketorolac is available by intravenous (IV) administration and is indicated for moderate to severe pain.[11 13 23] Ketorolac has strong analgesic and anti-inflammatory properties, but unlike opioids, it does not cause gastrointestinal dysmotility.[24 25] Ketorolac provides similar analgesia to opioids after outpatient surgical procedures associated with moderate pain such as fractures, hernia repair and tonsillectomy.[11 24] Even though ketorolac is commonly used in the ED for renal colic, lower back pain, abdominal pain, chest pain and migraine headaches,[26] all such use in children is off-label as there is a paucity of methodologically sound controlled trials of children to inform safe practice. Currently, 75% of drugs on the Canadian market lack any information on safety or dosing for use in children.[27] Despite calls from various paediatric societies[27 28] to reduce barriers to paediatric drug research, children continue to be largely excluded from clinical trials with only 6% of trials registered on clinicaltrials.gov focused on children.[29] The availability of an effective, safe, non-opioid analgesic that can be administered to children undergoing evaluation in the ED for appendicitis could diminish opioid use and consequent associated harms.[30] Given the current opioid crisis,[31] the undertreatment of pain in children and its adverse effects[32] and the lack of high certainty evidence on alternative analgesics for children with acute abdominal pain, there is an urgent need for a well-designed, rigorously conducted trial that will inform clinical treatment decisions and healthcare policy.

We previously reviewed 86 protocols for paediatric randomised controlled trials (RCTs),[33] and 127 protocols for surgical RCTs[34] that had been approved by ethics and begun recruitment. Of these, 40% and 43%, respectively, were discontinued before completion most often due to feasibility issues. Our proposed pilot trial will help us understand if there are feasibility issues that would present challenges to conducting a definitive trial. If so, we will modify our protocol to address these challenges. Our pilot study will also provide data which will help inform the sample size calculation for a definitive trial. If we do not make any significant changes to our protocol during the feasibility trial, we will consider this study vanguard and roll our pilot patients into a definitive study.

METHODS

We propose a pilot study to assess the feasibility of conducting a large definitive RCT to answer the following research question: In children aged 6–17 years presenting to a paediatric ED with ≤5 days of abdominal pain and undergoing investigations for suspected appendicitis, will administering IV ketorolac be non-inferior to IV morphine in reducing mean pain scores by a margin defined by the minimal important difference (MID)[16] of 2 from baseline, using the 11-point Verbal Numerical Rating Scale (VNRS)?[17] This will be a randomised, non-inferiority, double-dummy, blinded (participant, bedside clinicians, investigators and outcome assessors) double-blind, single-centre, feasibility, paediatric ED trial. Our study will adhere to recommendations from the 2010 Consolidated Standards of Reporting Trials (CONSORT) statement guidelines on feasibility pilot trials[35] (figure 1: CONSORT diagram).

Participant's eligibility criteria

Inclusion criteria and justification

1. Age 6–17 years: children <6 years of age are at low risk of appendicitis.[36 37]
2. Abdominal pain ≤5 days' duration: longer duration of pain is less likely to be appendicitis.[18 38]
3. A clinical decision to investigate for appendicitis (with blood work and/or ultrasound and/or paediatric surgery consult) as a possible aetiology by the clinical team or a confirmed appendicitis diagnosis made by the ED or paediatric surgery physician.
4. Patients who are initially assessed in our ED or are transferred from other sites.
5. Patients with IV cannula in situ or ordered to be placed: not to cause any additional pain or distress.
6. Currently experiencing moderate to severe pain: self-reported pain score ≥5 using the VNRS at the time of enrolment; ketorolac and morphine are used to treat moderate to severe pain.[39]

Exclusion criteria and justification

1. Previous enrolment in trial: to ensure all observations are independent and not paired.

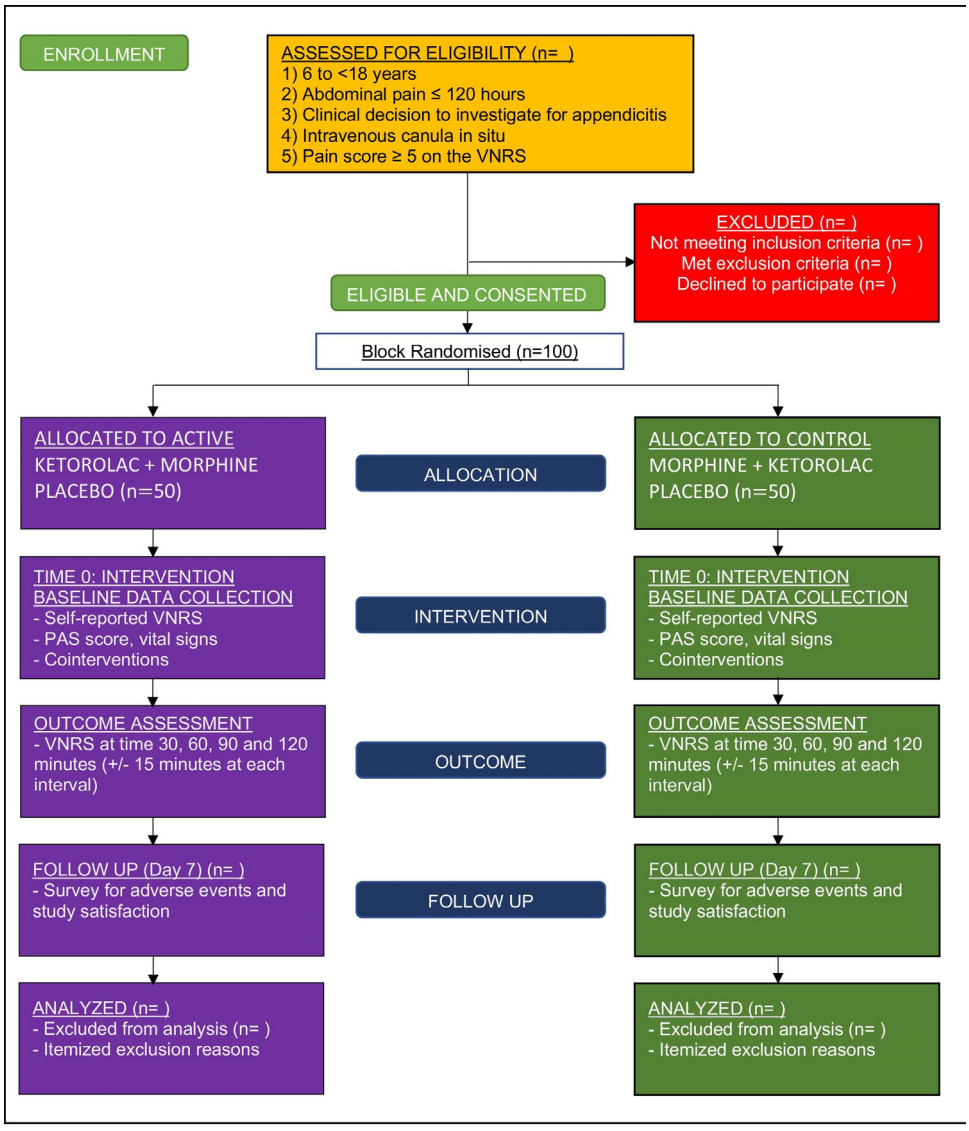

Figure 1 CONSORT diagram of study design. PAS is a validated clinical assessment score for patients with suspected appendicitis. CONSORT, Consolidated Standards of Reporting Trials; PAS, Paediatric Appendicitis Score; VNRS, 11-point Verbal Numerical Rating Scale (0–10).

2. NSAID use within 3 hours and/or opioid use within 2 hours prior to recruitment: to avoid overdosing and confounding.
3. Caregiver and/or child cognitive impairment precluding the ability to respond to study questions.
4. Chronic pain requiring daily analgesic use for other indications: confounding as response to analgesics may be altered.
5. History of gastrointestinal bleeding, peptic or duodenal ulcer disease or inflammatory bowel disease, coagulation disorders, prior cerebrovascular bleeding, known arteriovascular malformations: elevated bleeding risk with use of NSAIDs.[40]
6. History of chronic and active renal disease, excluding renal calculi and urinary tract infections.
7. History of chronic and active hepatocellular disease; ketorolac is metabolised in the liver.
8. Known pregnancy at the time of enrolment or breastfeeding women: there is a risk of premature closure of patent ductus arteriosus with NSAIDs.[41]
9. Known hypersensitivity to NSAIDs or opioids.
10. Absence of a parent/guardian for children who are <16 years in age.
11. Inability to obtain consent due to a language barrier and the absence of language translator in person or by a phone translation service available in the ED.

Planned interventions

(1) Active intervention group: IV ketorolac, 0.5 mg/kg to a maximum of 30 mg plus IV placebo (normal saline); and (2) active control group: IV morphine 0.1 mg/kg to a maximum of 5 mg plus IV placebo (normal saline). Rescue therapy will be allowed after 120 min of trial medication administration, and we will recommend morphine

0.05–0.1 mg/kg IV at the discretion of the treating physician.

Rationale for treatment dose

The doses used for both ketorolac and morphine are based on manufacturers and hospital drug monographs used in Canada and are indicated for moderate to severe pain. The acceptable dose range for ketorolac is 0.25–1 mg/kg/dose every 6 hours (maximum 30 mg/dose). Onset of action is 30 min after IV administration and the maximum effect is achieved at 2 hours, with a total duration of action up to 6 hours. Morphine dose for IV bolus use is 0.1 mg/kg up to a maximum of 5 mg/dose given every 2 hours. Onset of action is 5–10 min after IV administration and maximum effect is achieved at 20 min, with a total duration of action up to 4 hours.

Study procedures

The study's research pharmacist will generate a randomisation list using random varying blocks of 4 and 6 with a 1:1 allocation ratio. The research pharmacist will prepare consecutively numbered study drug vials according to the randomisation schedule. At least two study drug kits will be stored in the medication dispensing room at the ED and be replenished as needed by the research pharmacist. Only the research pharmacist will retain the randomisation code. Children identified as potentially eligible for the study or the medical directive by triage nurses, bedside nurses or treating physicians will be screened by the clinical research assistant (CRA) for eligibility. Details of the study will be discussed with eligible participants and their caregivers. Once caregivers consent and participants assent (for children ≥7 years in age), the CRA will access REDCap to register the patient and enter the assigned subsequent drug kit number. A log of all screened patients will be maintained.

The CRA will collect baseline clinical variables and will complete the data collection forms. Elements of baseline pain severity (assessed by VNRS), location of pain, duration of pain since onset, associated symptoms (eg, nausea, anorexia, vomiting, dysuria, fever, pain with movement, Paediatric Appendicitis Score) will be collected. The CRA will give the next consequentially numbered drug kit to the clinical nurse with carefully labelled vials and dosing guidelines to administer as a push or a pump over 5 min as per the hospital drug monograph instructions for both drugs. Time 0 will be the time study drug administration is completed.

Our study drug kits will contain either active ketorolac and placebo morphine or active morphine and placebo ketorolac. The study drugs and placebo will be identical in appearance, consistency and smell. Vials will contain clear liquid ketorolac 10 mg/mL or morphine 2 mg/mL with their respective normal saline placebos. Placebos will be identical in appearance, volume and consistency (normal saline). The double-dummy design will ensure blinding of the nurses who are drawing up and administering the drug, as the per kilogram dose, is different for morphine and ketorolac. Physicians, nurses, participants and their families, investigators and research assistants will be blinded to prevent bias in trial procedures and outcome assessment. Once patients are randomised, pharmacological co-interventions directed at pain relief will be limited to acetaminophen. However, all other non-analgesic pharmacotherapy will not be restricted and can be administered at the discretion of the responsible physician.

During the ED visit, all clinical outcomes will be measured within 2 hours of receiving the intervention. Further, ED and inpatient chart reviews will be completed to determine any adverse events, total doses of opioids administered in morphine equivalents/kg, type of NSAIDs administered and dose/frequency for each and the final diagnosis assigned. A phone or electronic parent/caregiver survey will be administered 7–14 days after discharge to elicit any change in diagnosis, late adverse events and satisfaction with study procedures.

Emergency unblinding

In the unlikely event that a treating physician feels that unblinding is required to inform clinical care, a request will be made to unblind to the CRA and/or the principal investigator (PI) for approval. Once approved, we will have sealed opaque envelopes that have corresponding labels for every drug kit. Those opaque envelopes will have a written document with the active drug in every drug kit. They will be stored separately from the drug kits outside of the ED in an office space that is locked by door and cabinet. Envelopes can only be retrieved by CRA or a delegated research assistant. Upon completion of the trial, all envelopes will be returned to research pharmacy with the used and unused drug kits to check the seal on the envelopes and document any unblinding. All accidental or intentional unblinding will be documented and reported to the PI. Patients whose treatment allocation is unblinded will remain in the study.

Outcomes

Feasibility outcomes

Our primary feasibility outcome is the proportion of eligible patients approached who provide informed consent and are enrolled in our trial. We will also assess the proportion of participants who: ; (1) complete their clinical outcome assessments and (2) have missing items on individual data collection forms. Additional feasibility outcomes include: (3) proportion of participants/caregivers who were satisfied with study procedures and interventions based on the 11-point Verbal Numerical Scale and if they would be willing to participate in a future trial; (4) reasons for declining consent; (5) reasons for withdrawing consent; (6) proportion of participants who complete the study fully (baseline characteristics, outcome assessment and follow-up survey) and (7) frequency of protocol deviations, specifically consecutive assignments of drug kits (table 1: summary table).

Table 1 Trial feasibility and clinical outcomes

Outcome		Measure	Thresholds* and analysis
Feasibility outcomes	Participant recruitment	Consent rate	≥40% of subjects approached
		Proportion of eligible patients approached for consent	≥50% of eligible subjects
		Recruitment/month	≥8/month on average over 1 year
	Participant eligibility	Proportion meeting eligibility	≥70% of subjects clinically investigated for appendicitis
	Participant retention	Proportion completed outcome assessment	≥90% of participants
	Completion of study material	Proportion of participants who completed outcome assessment at all time points	≥90% of participants
		Proportion of missing items on individual data collection forms (screening forms, baseline characteristics, outcome assessment, follow-up survey)	<10% of missing items
	Participants' satisfaction	Proportion of participants and caregivers who were satisfied with study procedures and interventions, on a 0–11 numerical satisfaction survey	≥70% of participants score ≥7/10
Clinical outcomes	Improvement in pain score	Self-reported 11-point VNRS pain scores at 30, 60, 90, 120 min	Linear regression
	Improvement in category of pain	Proportion of participants with a change in their baseline pain category Mild pain: VNRS <5 Moderate pain: ≥5–7 Severe pain: ≥8	Logistic regression
	Proportion of participants who achieved their desired pain state	A 0–10 numerical satisfaction scale	Linear regression
	Time to effective analgesia	Time it takes to achieve a pain score <3/10	Survival analysis in each group individually
	Rescue analgesia	Proportion of participants who received rescue analgesia (morphine) in each trial arm measured in morphine equivalent mg/kg within 6 hours of intervention	Logistic regression
	Missed appendicitis	Frequency of appendicitis diagnosed on a return visit within 7 days	Logistic regression
	Adverse event profile	The proportion of children with any adverse events related to study drug administration with attention to heart burn, chest pain, epigastric pain, nausea, vomiting, dizziness, rash, haematuria, headaches and pruritus	Logistic regression

*All feasibility outcomes and thresholds will be analysed using descriptive statistics.
VNRS, Verbal Numerical Rating Scale.

Clinical outcomes

Clinical outcomes will be exploratory since our feasibility trial will be underpowered to detect differences in treatment effects. Clinical outcomes will include: (1) pain relief as measured on the 11-point VNRS at baseline and at 30, 60, 90 and 120 min after drug administration; (2) proportion of participants who change their baseline pain category at all time points (mild 1–3, moderate 4–6, severe ≥7 on VNRS)[42]; (3) pain score and time at which any further analgesia is declined (eg, participant achieved desired pain state)[42]; (4) time to effective analgesia (ie, VNRS <3); (5) proportion of participants requiring any rescue analgesia in each trial arm and the total amount of opioid administered as measured by morphine equivalent mg/kg within 8 hours of intervention; and (6) frequency of missed appendicitis (from the chart review and the follow-up call 7–14 days).

Adverse events profile

The proportion of children experiencing any adverse events, as reported by caregivers or clinical staff, will be recorded. We will solicit adverse events and code them using the Medical Dictionary for Regulatory Activities. This serves as a 'single standardised international medical terminology which can be used for regulatory communication and evaluation of data pertaining to medicinal products for human use'.[43]

Sample size

Our main criterion of success will be to enrol ≥40% of eligible patients who are approached. This is a conservative estimate compared with 60% consent rates in prior placebo-controlled acute pain ED studies and current trials in the McMaster Children's Hospital ED.[4 6 44 45] Using a 95% CI for the proportion of eligible patients enrolled in our study and a margin of error of 0.1, a lower bound of this confidence of 0.3 and an expected enrolment rate of 40%, the minimum required sample for the pilot study would be 100 participants.[46]

Trial pain scale

The 11-point VNRS is a validated self-reported acute pain scale for which an anchor-based MID of 2 points has been established.[42 47] The VNRS has strong convergent validity, known-groups validity, responsivity, and test–retest reliability in children 6–17 years old with acute pain and in

the emergency setting.[42 47] It is rapidly administered by asking 'On a scale of 0–10, 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 in children, the VNRS was the only pain scale that received a strong recommendation for use in children ≥6 years in age.[48]

Planned analysis

Descriptive and exploratory analyses will be done for each feasibility objective. All participants who are randomised will be included in our analyses (ie, intention-to-treat). Participants who discontinued the study early (discharged or went to operating room) will be included with reasons for discontinuation documented. Patients' baseline characteristics will be tabulated and described using frequency counts and percentages for dichotomous or categorical data, and continuous variables will be described using means and SDs, or medians and IQRs, depending on distribution. Statistical analyses will be performed using SAS V.9.2 (SAS Institute).

Feasibility outcome analyses and criteria for progression

Quantitative analyses will enable us to assess our data against the following feasibility criteria we seek to meet within reasonable limits:

1. Recruit ≥40% of eligible patients who were approached for consent.
2. Recruit ≥8 participants/month averaged over the duration of the trial.
3. At least 90% of participants complete the 11-point VNRS for pain at 30, 60, 90 and 120 min within 15 min of the desired time point.
4. At least 90% overall data completion rate.
5. At least 70% of participants are satisfied with study procedures (scored ≥5 on an 11-point Numerical Rating Scale) and ≥70% would participate in a future trial.

We will base our decision to progress to a definitive trial on the direct measure of the proportion for criterion 1 as well as a 95% CI estimate with a margin of error of 0.1. If we are below our progression threshold, we will identify the barriers to enrolment (eg, strict eligibility criteria, CRA hours of coverage, participants refusing blinding) of eligible patients and adjust the final study protocol accordingly. If there are no identifiable barriers, we will deem a definitive trial to be non-feasible. This decision will be made by the trial steering committee. For criteria 2–6, we will report on counts, frequencies and proportions and describe differences in proportions between groups. We will construct an estimate for the error using the 95% CI for proportions and means.

Clinical outcome analysis

Since this is a feasibility pilot trial, no formal hypothesis testing for efficacy will be conducted. For the definitive trial, we will base our sample size on the established MID for the 11-point VNRS (2 points), a non-inferiority margin of 1 point (50% of MID) and the variance around treatment effect observed in the pilot trial.[49] The change in pain scores over chosen time intervals will help us determine the best time interval for evaluating our primary outcome in the definitive trial. We will calculate the within-group means of pain reduction by using linear regression for the VNRS continuous scale. We will use logistic regression for proportions of participants who changed pain category and required rescue analgesics. Baseline pain scores will be entered as a covariate.

Adverse event profile analysis

The proportion of children experiencing any adverse events, as reported by caregivers, physicians or nurses, will be compared between groups using descriptive statistics and logistic regression if the number of events allows. The analysis will evaluate the presence/absence of side effects in each group (table 1: outcome summary table).

Planned subgroup analysis

To inform feasibility and design of the future trial, we will conduct an exploratory analysis to see if the enrolment rate is different among (1) participant sex; (2) participant gender; (3) time of day, between 10:00–<16:00 and 16:00–22:00; and (4) participants' final surgical diagnoses of appendicitis (received appendectomy or treated with IV antibiotics) versus not. Biological mechanisms, such as sex hormones, influence the nervous system perception of pain and response to analgesics.[36–38] In addition, gender norms are known to impact a patient's perceived sensitivity to pain. After explaining to participants and caregivers why sex and gender are important in pain research, we will use the recommended[50] two-step questionnaire to determine biological sex and gender separately. The two-step survey has been tested in transgender populations and validated over a broader North American population.[51–55]

Clinical monitoring, safety monitoring, quality assurance and quality control

This study may be subject to audit or inspection by representatives of the research office at Hamilton Health Sciences or representatives of Health Canada. Privacy and confidentiality policy and procedure will also be reviewed at the study recruitment training session for all study personnel. Clinical site monitoring is conducted to ensure that the rights and well-being of trial participants are protected, that the reported trial data are accurate, complete, and verifiable, and that the conduct of the trial is in compliance with the currently approved protocol/amendment(s), with International Conference on Harmonisation Good Clinical Practice, Tri-Council Policy Statement 2 and with applicable regulatory requirement(s) (eg, Health Canada). The PI and McMaster Children's Hospital will permit trial-related monitoring, audits, Research Ethics Board (REB) review and regulatory inspection(s) by providing direct access to source data/documentation, as required.

Our study will be monitored by a Data Safety and Monitoring Board (DSMB). Since this is a feasibility trial, there will be no specific stopping rules. The DSMB will be looking at safety and trial recruitment process and advise the steering committee on possible protocol modification to maintain safety, trial integrity and increase feasibility. We will inform the DSMB and Health Canada of all serious adverse events within 7 days of their occurrence. If the DSMB has any safety concerns, they may request unmasking. The DSMB will be completely independent from the trial steering committee and will have a clinical ED physician, a clinical researcher and a biostatistician with no association with trial sponsor or PI.

Patient and public involvement

During the early stages of study question conceptualisation and design, we have engaged our local hospital family advisory council constituting of 14 caregivers, a child life specialist and hospital leadership. A formal presentation was done on all aspects of the study including the research question, design, recruitment strategy and outcome measures. The family advisory council determined that a trial that has the potential to reduce opioid use in the ED should be a major priority. Several members' quotes include 'anything to reduce use of opioids with kids has my blessing, this is so important to find alternatives to opioids' and 'we need to curb the use of opioids every chance we get, especially in our children to avoid long-term addictions/consequences'. There was no additional feedback to change the randomisation sequence generation, blinding or allocation procedures. The chair of the family advisory council reviewed the protocol (KB) and assisted us in drafting lay summaries, posters for advertisement and consent as well as assent forms (see online supplemental file 1). To further integrate patient involvement in the development of our definitive trial, we designed a survey to be administered 7 days after our trial to assess if patients/caregivers were satisfied with the study procedures and illicit feedback on any changes that should be made. The completed feasibility trial publication will be shared with study participants.

Future direction

To our knowledge, this is the first trial in children with suspected appendicitis comparing IV morphine with ketorolac. We will determine if a definitive, multicentre trial of ketorolac versus morphine for acute pain among children with suspected appendicitis is feasible by specifically: (1) assessing the pragmatic sensibility of our eligibility criteria and ensure we are able to recruit enough patients by enrolling ≥40% of eligible patients approached; (2) testing our randomisation and data collection procedures; (3) collecting information on associated adverse events linked to inform the focus of our safety assessment; (4) garnering feedback from clinicians and participants on study design and (5) presenting our findings at the annual Pediatric Emergency Research Canada (PERC)[43] conference in order to solicit feedback and engage other sites and stakeholders to collaborate in our planned future multicentre trial. If our pilot trial is successful based on feasibility thresholds and does not require any significant changes to the protocol, we will include the clinical outcome data in the analysis of the definitive trial.

We anticipate that our trial will be feasible. Our team is multidisciplinary with expertise in international network trials (SF, SA, JWB, RC, LT), pharmacological pain trials (SA, JWB) and feasibility and non-inferiority designs (LT). In terms of completing the clinical outcome assessment, a similar pain trial (the OUCH trial[15 56]) achieved a 90% rate of complete follow-up. We therefore expect a similar rate of follow-up in our proposed trial. The average time to disposition (discharge or admission) at McMaster Children's Hospital for children who are investigated for appendicitis is 5.5 hours which provides ample time for intervention and primary outcome assessment. A $10 gift card will be given to participating families who complete all secondary outcome assessments.

ETHICS AND DISSEMINATION

We have obtained full ethics approval from Hamilton integrated REB (certificate 12957) as well as a Health Canada approval for our trial. Any protocol amendments will be communicated to the REB and updated on the trial registry site (https://clinicaltrials.gov/ct2/show/NCT04528563). To promote uptake of our study outputs, we have engaged relevant stakeholders in appropriate and meaningful ways throughout the project. Creating partnerships with our hospital family advisory council, surgical programme, PERC, Solutions for Kids in Pain from idea conceptualisation to background work and feasibility assessment to definitive trial completion will maximise collaboration and enhance the interaction between knowledge users at different phases of research. We will submit the results of our completed trial for poster and oral presentation to annual paediatric (Canadian Pediatric Society), emergency (Canadian Association of Emergency Physicians) and pain association (Canadian Pain Society) conferences, and for publication in a peer-reviewed journal.

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Competing interests None declared.

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Consent (for participants aged 16-17 y)

A Pilot Randomized Non-Inferiority Trial of Ketorolac vs. Morphine in Children with Suspected Appendicitis

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Funding Source: Hamilton Health Sciences New Investigator Fund

You are being invited to participate in a research study because we think you might have appendicitis. This letter gives you information about the study. We will talk to you about the letter. You don't have to be in the study if you don't want to. Please read this letter carefully and ask us any questions. All your questions should be answered before you decide if you want to be in the study. The care you get at the hospital will not change if you are in the study or not. We will be asking at least 100 children to be in the study.

Why is this research study being done?

The appendix is a small finger-shaped sack that is connected to the large intestine (colon) on one side only. Sometimes the tube between the appendix and the colon gets blocked. This can cause the appendix to become infected and inflamed – we call this appendicitis. This can cause children to have very bad pain in their belly. Sometimes they will even feel sick, throw up or not want to eat or drink. To treat appendicitis, some children will need surgery which means they will need to stop eating and drinking. Pain medicine can be given medicine through a needle called an intravenous or IV. Among other pain medications, the most common IV pain medicine given for this condition is ketorolac and morphine.

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Morphine is used for more than half of all children who may need surgery. Another word for morphine is Opioid. The rest of the children get another pain medication like ketorolac, a non-steroidal anti-inflammatory drug (NSAID). Ketorolac causes few side effects when it is used for a short period of time. It does not cause drowsiness or problems with going poo like morphine does.

In our emergency department, we use ketorolac for painful problems like kidney and gall bladder stones, migraine headaches, appendicitis, pains from a period and joint pains. We know from a few studies that it might be just as good as morphine to help with pain. This would mean we might not need to use morphine. Even though we know ketorolac well, we do not have good studies that can tell us how it compares to morphine for helping children with appendicitis. At a time when we are trying to use morphine less, we need to show that there are choices to help children with pain that are just as good or better and have only small side effects.

The goal of this study is to see if ketorolac works just as well as morphine in helping with pain in children with appendicitis. We also need to know if children who get ketorolac have less side effects than children who get morphine. The first step in doing a big study like this means that first we need to a smaller one at McMaster Children's Hospital to sort out all the possible problems. To answer this research question, we will need a large number of patients in a study. To get enough patients, we must include many hospitals in different cities and provinces to run the same study. The goal of doing this at McMaster first is to make sure our study is able to recruit enough people over an acceptable time frame and that all the information we collect is complete and nothing is missing.

What will happen during this research study?
If you agree to participate in this study, you will get pain medicine through a needle. You will get morphine or ketorolac. Only the hospital pharmacist will know which medicine you got. If there is a reason that the doctor needs to find out which medicine you got (like if you have an unexpected allergic reaction), the doctor will find out. At the end of the entire study, the researcher in charge of the study will know which medication you got.

Being in the study means we need to ask you how your pain is after you get the medicine. We will do this by asking you "On a scale of 0 to 10, where 0 means no pain and 10 means the worst pain, how much do you have right now?". After you have been home for 7 days, we will call you or your family or send an email to ask if you had any side effects after you went home. We also want to know if you and your caregiver are happy with how the study went.

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What are the risks/benefits to doing this research study?
The risks in participating in this study are no different than if you were not in the study. You will get a needle for the pain medicine even if you are not in this study. Should you receive intravenous ketorolac, the common side effects may include nausea, upset stomach, headache, itching, or rash or pain at the IV site. Rarely or with prolonged usage, you may get a stomach ulcer or bleeding or an allergic reaction. If you are receiving morphine, common side effects may include nausea, vomiting, constipation, itching, dizziness/drowsiness or headache or rash or pain at the IV site. Rarely, you may experience an allergic reaction or difficulty breathing. All patients in the study can take acetaminophen (Tylenol) if they need to. If you have bad pain after you get the study medication, more pain medicine will be available to give (morphine).

How will I be compensated?
There are gift vouchers given to you as a token of appreciation for completing the study survey.

How could I withdraw from the research study?
If you wish to stop participating in the study, you can do so at any time by contacting the study researchers Dr. Mohamed Eltorki (905 521 2100 extension 76472 or at eltorkim@mcmaster.ca), or the study coordinator Redjana Carciumaru (905-521-2100 extension 73864 or at carciur@mcmaster.ca)

How will the information we collect be kept private?
All the information you provide will be confidential (private), and will only be seen by this project's researchers. The information will be stored in a locked database that will not have your name or any other information that may be used to directly identify you. Following completion of the study, data will be kept in a secure location for a minimum of 25 years as per the requirements of regulatory authorities.

How do I find out what was learned in the research study?
If you decide to participate in the study, and wish to know the outcome of the study, we would be happy to provide you a copy of the results.

What happens if you have a research-related injury?
There is very small risk of injury from being in this research study. If there is an injury related to the study, you will be treated and there will be no cost. Financial compensation for such things as lost wages, disability or discomfort due to this type of injury is not routinely available. However, if you sign this consent form it does not mean that you waive any legal rights you may

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have under the law, nor does it mean that you are releasing the investigators from their legal and professional responsibilities.
For the purposes of ensuring the proper monitoring of the research study, it is possible that a member of any institutional regulatory body, the Hamilton Integrated Research Ethics Board, and a Health Canada representative may consult your child's research data and medical records. However, no records which identify your child by name or initials will be allowed to leave the hospital. By signing this consent form, you authorize such access.
This study has been reviewed by the Hamilton Integrated Research Ethics Board (HiREB). The REB is responsible for ensuring that participants are informed of the risks associated with the research, and that participants are free to decide if participation is right for them. If you have any questions about your rights as a research participant, please call The Office of the Chair, HiREB at (905) 521 2100 x 42013.

Consent:
I understand the nature of the project explained to me, including all of the potential benefits and risks, hereby agree to participate in the study. I will receive a signed copy of this consent form.

_____	_____	_____
(print name of participant)	*(signature of participant)*	*(date yyyy/mm/dd)*

I have explained to the participant's caregiver all aspects pertaining to this study and I have answered the questions that they have asked me. I have indicated to them that participation in the study is voluntary and that they may withdraw at any time.

_____	_____	_____
(print name of person obtaining consent)	*(signature of person obtaining consent)*	*(date yyyy/mm/dd)*

The research project must be explained to the caregiver and the participant and a member of the research team must answer their questions, specifying that participation in the project is free and voluntary. The research team will respect the terms of the consent form.

_____	_____	_____
(print name of researcher)	*(signature of researcher)*	*(date yyyy/mm/dd)*

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Consent (for Caregiver)

A Pilot Randomized Non-Inferiority Trial of Ketorolac vs. Morphine in Children With Suspected Appendicitis

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Lehane Thabane, PhD, McMaster University, Hamilton, Ontario

Funding Source: Hamilton Health Sciences New Investigator Fund

Your child is being invited to participate in a research study because they have belly pain from possible appendicitis. This form gives you information about the study. Someone will talk to you about the study so you can decide if you want to be in it. Please read this form carefully and ask any questions you may have. Make sure you have all your questions answered before you decide if you want to be a part of the study. The care your child will get at the hospital will not be affected if you choose not to be part of it. At least 100 children will be in the study.

Why is this research study being done?

The appendix is a small finger-shaped sack that is connected to the large intestine (colon) on one side only. Sometimes the tube between the appendix and the colon gets blocked. This can cause the appendix to become infected and inflamed – we call this appendicitis. This can cause children to have very bad pain in their belly. Sometimes they will even feel sick, throw up or not want to eat or drink. To treat appendicitis, some children will need surgery which means they will need to stop eating and drinking. Pain medicine can be given medicine through a

needle called an intravenous or IV. Among other pain medications, the most common IV pain medicine given for this condition is ketorolac and morphine.
Morphine is used for more than half of all children who may need surgery. Another word for morphine is Opioid. The rest of the children get another pain medication like ketorolac, a non-steroidal anti-inflammatory drug (NSAID). Ketorolac causes few side effects when it is used for a short period of time. It does not cause drowsiness or problems with going poo like morphine does.

In our emergency department, we use ketorolac for painful problems like kidney and gall bladder stones, migraine headaches, appendicitis, pains from a period and joint pains. We know from a few studies that it might be just as good as morphine to help with pain. This would mean we might not need to use morphine. Even though we know ketorolac well, we do not have good studies that can tell us how it compares to morphine for helping children with appendicitis. At a time when we are trying to use morphine less, we need to show that there are choices to help children with pain that are just as good or better and have only small side effects.

The goal of this research is to see if ketorolac works just as well as morphine in helping with pain in children with appendicitis. We also need to know if children who get ketorolac have less side effects than children who get morphine. The first step in doing a big study like this means that first we need to a smaller one at McMaster Children's Hospital to sort out all the possible problems. To answer this research question, we will need a large number of patients in a study. To get enough patients, we must include many hospitals in different cities and provinces to run the same study. The goal of doing this at McMaster first is to make sure our study is able to recruit enough people over an acceptable time frame and that all the information we collect is complete and nothing is missing.

What will happen during this research study?
If you decide to be in this study, your child will receive pain medicine through the intravenous. They will get either ketorolac or morphine to treat their pain. The decision on which one they will get will be random, just like flipping a coin. No one will know which medicine your child will get except the hospital pharmacist. Your child, you, doctors, nurses and research staff will not know which medicine your child is getting, unless the doctor needs to know for special reasons (example: your child had a rare or unexpected allergic reaction). At the end of the study, after 100 children have been in it, the doctor in charge of the study will find out which medicine each child received.

In order to know if the pain medicine is working, we will measure your child's pain. This is done by asking your child "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?" We will ask this question a few times while your child is getting the medicine. Then, after your child has been home for 7 days, we will call you or send you an email to ask if your child had any side effects after they went home. We will also ask if you and your child were happy with how the study went.

What are the risks/benefits to doing this research study?
The risks of being in this study are no different than any risk you would have if you weren't in the study. This is because your child will get pain medicine with intravenous even if you did not participate. Should you receive intravenous ketorolac, the common side effects may include nausea, upset stomach, headache, itching, or rash or pain at the IV site. Rarely or with prolonged usage, you may get a stomach ulcer or bleeding or an allergic reaction. If you are receiving morphine, common side effects may include nausea, vomiting, constipation, itching, dizziness/drowsiness or headache or rash or pain at the IV site. Rarely, you may experience an allergic reaction or difficulty breathing. All children who participate are allowed to take acetaminophen (Tylenol) if they need to. If your child has bad pain after they get their medicine, we will be able to give them more pain medicine (morphine). Your child will receive appropriate attention during the study.

How will I be compensated?
If you choose to participate, we will thank you by giving you a gift card at the end of the study.

How can I withdraw from the research study?
If you wish to stop being in the study, you can call the study researchers at any time: Dr. Mohamed Eltorki (905 521 2100 extension 76472 or at eltorkim@mcmaster.ca), or the study coordinator Redjana Carciumaru (905-521-2100 extension 73864 or at carciur@mcmaster.ca).

How will the information we collect be kept private?
All the information you give us will be confidential (private). Only the study's research team will be see the information. The information will be stored on a computer that will not have your child's name or any other information that may be used to identify your or your child. Following completion of the study, data will be kept in a secure location for a minimum of 25 years as per the requirements of regulatory authorities.

How do I find out what was learned in the research study?
If you decide to be in the study, we would be happy to provide you a copy of the results.

What happens if my child has a research-related injury?
There is very small risk of injury from being in this research study. If there is an injury related to the study, your child will be treated and there will be no cost. Financial compensation for such things as lost wages, disability or discomfort due to this type of injury is not routinely available. However, if you sign this consent form it does not mean that you waive any legal rights you may have under the law, nor does it mean that you are releasing the investigators from their legal and professional responsibilities.

For the purposes of ensuring the proper monitoring of the research study, it is possible that a member of any institutional regulatory body, the Hamilton Integrated Research Ethics Board,

and a Health Canada representative may consult your child's research data and medical records. However, no records which identify your child by name or initials will be allowed to leave the hospital. By signing this consent form, you authorize such access.

This study has been reviewed by the Hamilton Integrated Research Ethics Board (HiREB). The REB is responsible for ensuring that participants are informed of the risks associated with the research, and that participants are free to decide if participation is right for them. If you have any questions about your rights as a research participant, please call The Office of the Chair, HiREB at (905) 521 2100 x 42013.

Consent:
I understand the nature of the project explained to me, including all of the potential benefits and risks, hereby agree to participate in the study. I will receive a signed copy of this consent form.

_____	_____	_____
(print name of caregiver)	*(signature of caregiver)*	*(date yyyy/mm/dd)*

I have explained to the participant's caregiver all aspects pertaining to this study and I have answered the questions that they have asked me. I have indicated to them that participation in the study is voluntary and that they may withdraw at any time.

_____	_____	_____
(print name of person obtaining consent)	*(signature of person obtaining consent)*	*(date yyyy/mm/dd)*

The research project must be explained to the caregiver and the participant and a member of the research team must answer their questions, specifying that participation in the project is free and voluntary. The research team will respect the terms of the consent form.

_____	_____	_____
(print name of researcher)	*(signature of researcher)*	*(date yyyy/mm/dd)*

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Assent (for participants aged 7-15 y)

A Pilot Randomized Non-Inferiority Trial Of Ketorolac Vs. Morphine In Children With Suspected Appendicitis

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Lehane Thabane, PhD, McMaster University, Hamilton, Ontario

Funding Source: Hamilton Health Sciences New Investigator Fund

Why are we doing this study?

Sometimes children may have tummy pain that can be caused by appendicitis. Appendicitis means that a small piece of your intestine, located in your tummy, is swollen and inflamed, kind of like it is upset or angry. This can make the tummy very sore and can even make children sick to their tummy. Sometimes children can't eat or drink. Children can take medicine to help with the pain they feel. If a child needs an operation to help their appendicitis, they can't eat or drink before the operation.

There are many types of medicines that doctors can give children to help with their tummy pain. Our study is going to compare two types of these medicines, that are regularly used, to see which one is better or if they are the same.

Why am I being asked to be in the study?

We are asking you to be in the study because you came to the Emergency Department with tummy pain. We are trying to learn more about treating bad tummy pain in children. If you want to be in the study, you will help doctors understand what the best medicine is to give to children like you.

If I am in the study, what will happen to me?
A nurse or a doctor will give you medicine through a needle. Then we will come back to see you a few times and ask you how sore your tummy is. We will ask: "From 0 to 10, where 0 means no pain and 10 means the worst pain, how much do you have right now?"

What if I have questions?
You can ask me any questions that you have about this study. Even if you have questions later, you can call or email the doctor. His phone number is 905-521-2100 ext.76472 and his email is eltorkim@mcmaster.ca.

Will I be hurt if I am in the study?
We will give you pain medicine through a needle. Even if you were not in the study, you would still get the needle. This is because it's the best way to give you pain medicine. Being in the study will not mean you get any more needles.

Will the study help me?
If you are in the study, it may help you feel better. You will have more people looking after you and checking that your tummy pain is getting better. Also, you will be helping other kids that come to the hospital because we will know more about how to treat their tummy pain. You will receive a small gift from us as a thank you for participating in our study.

Do I have to be in this study?
You do not have to be in this study if you do not want to be. If you decide that you don't want to be in this study it is OK. Nobody will be angry or upset. We also talked to your parent/caregiver about this study, and you should talk to them too.

What happens after the study?
When we are all finished with the study, we will write a report about what we learned. This report will not have your name or tell that you were in this study.
If you decide you want to be in this study, please print/write your name. You will receive a signed copy of this consent form.

_____	_____	_____
(print name of participant)	*(Initials of participant)*	*(date yyyy/mm/dd)*

I have explained to the participant's caregiver all aspects pertaining to this study and I have answered the questions that they have asked me. I have indicated to them that participation in the study is voluntary and that they may withdraw at any time.

_____	_____	_____
(print name of person obtaining consent)	*(signature of person obtaining consent)*	*(date yyyy/mm/dd)*