IRB#	NCT#	Version Date	Study Title
2022-0640	**NCT05664074**	**03.13.23**	**Post-ERCP Pancreatitis Prophylaxis, Effectiveness of Rectal Indomethacin vs Intravenous Ketorolac in the Pediatric Population**

Study Title: Post-ERCP Pancreatitis Prophylaxis, Effectiveness of Rectal Indomethacin vs Intravenous Ketorolac in the Pediatric Population

Principal Investigator: David S. Vitale

Sub-Investigators: Sherif Y. Ibrahim, Tom K. Lin, Lindsey Hornung, Ethan Estes, Tyler Thompson, Lin Fei, Maisam Abu-El-Haija

1.0 Background

Endoscopic retrograde cholangiopancreatography (ERCP) is an essential interventional procedure but can be complicated by post-ERCP pancreatitis (PEP). Rectal indomethacin has been shown to reduce rates of PEP adult populations and a recent study showed reduced rates of PEP in pediatric patients receiving intravenous (IV) ketorolac in a retrospective study[1]. There have been no studies comparing the effectiveness of these prophylactic medications in preventing PEP in pediatric patients. Both rectal indomethacin and IV ketorolac are currently standards of care. In a retrospective analysis at our institution involving 80 ERCPs for 57 unique patients, when directly comparing medication prophylaxis, the odds of developing PEP were 3.4 times higher for those given rectal indomethacin compared to those given IV ketorolac (OR 3.4, CI 0.6-21.2). Additionally, a variety of risk factors can be associated with PEP and rates can vary. Particularly in high-risk patients with pancreatic duct injection, ketorolac was more effective than indomethacin in preventing PEP (IV ketorolac OR of 0.5 and Rectal indomethacin OR of 3.8) in our retrospective analysis. Unfortunately, this study was a retrospective analysis with limited sample size. Therefore, further studies are required to help identify possible modalities to improve rates of PEP and patient outcomes.

Purpose:

1. To compare effectiveness of therapy with rectal indomethacin versus IV ketorolac in affecting the rate of PEP.
2. To identify risk factors associated with increased rates of PEP in pediatric patients who underwent ERCP for pancreatic or biliary indications, and to review the effectiveness of techniques commonly employed to prevent PEP.
3. To identify possible biomarkers to predict PEP.

1.1 Clinical Relevance

ERCP is a safe and beneficial therapeutic option in treatment of children with pancreatobiliary disease but can be complicated by PEP in up to 10 - 20% in high risk patients [2]. Ketorolac and indomethacin are both viable options for prophylaxis but the superior modality has not been studied in the pediatric population.

1.2 Definitions

We will use the Classification of Acute Pancreatitis in the Pediatric Population: Clinical Report from the North American Society for Pediatric Gastroenterology, Hepatology & Nutrition (NASPGHAN) Pancreas Committee to define Acute Pancreatitis and severity of Acute Pancreatitis. [3]

1. Acute Pancreatitis (AP): We will use the previously established definition of pediatric AP. A patient must have at least 2 of the following to establish a diagnosis of AP:

a. Characteristic physical exam findings- pain worse than admission per pain scales (please see point 4 and 5 below) and/or nausea

b. Amylase or lipase greater than 3 times the age appropriate upper limit of normal

c. Confirmatory imaging (Ultrasound, CT or MRI) that suggests or demonstrates pancreatic inflammation

2. Severity of AP: Severity of AP in patients in this study will be classified as mild, moderately severe, or severe in accordance with the NASPGHAN Classification system. The following definitions in quotations are taken directly from this source.

a. Mild: "AP that is not associated with any organ failure, local or systemic complications, and usually resolves within the first week after presentation."

b. Moderately Severe: "AP with either the development of transient organ failure/dysfunction (lasting no >48 hours) or development of local or systemic complications. Local complications would include development of (peri) or pancreatic complications including fluid collections or necrosis. Systemic complications would include exacerbation of previously diagnosed co-morbid disease (such as lung disease or kidney disease)."

c. Severe: "AP with development of organ dysfunction per International pediatric sepsis consensus conference (please see definition 9) that persists >48 hours. Persistent organ failure may be single or multiple, and may develop beyond the first 48 hours of presentation."

3. Post ERCP Pancreatitis (PEP): Defined as development of AP within 2 weeks of ERCP per American Society for Gastrointestinal Endoscopy (ASGE) guidelines[4].

4. Face, Legs, Activity, Cry, and Consolability (FLACC): Pain scale for patients 0-5 years of age and patients unable to verbalize pain [5]

Table 1. FLACC pain scale

Criteria	Score 0	Score 1	Score 2
Face	No particular expression or smile	Occasional grimace or frown, withdrawn, uninterested	Frequent to constant quivering chin, clenched jaw
Legs	Normal position or relaxed	Uneasy, restless, tense	Kicking, or legs drawn up
Activity	Lying quietly, normal position, moves easily	Squirming, shifting, back and forth, tense	Arched, rigid or jerking
Cry	No cry (awake or asleep)	Moans or whimpers; occasional complaint	Crying steadily, screams or sobs, frequent complaints
Consolability	Content, relaxed	Reassured by occasional touching, hugging or being talked to, distractible	Difficult to console or comfort

5. Numeric Rating Scale (NRS) Pain scale for patients 6 years old and above [6]

a. Mild- 0 to 3

b. Moderate- 4 to 6

c. Severe- 7 to 10

6. Acute Kidney Injury:

Per Kidney Disease: Improving Global Outcomes (KDIGO)

a. Increase in serum creatinine $\geq$ 0.3 mg/dL from baseline within 48 hours

b. Increase in serum creatinine to $\geq$ 1.5 tune baseline within the prior 7 days

c. Urine volume $\leq$0.5 mL/kg/hour for 6 hours

7. Chronic Kidney Disease per KDIGO:

a. Glomerular filtration rate (GFR) less than 60 mL/min per 1.73 m^2 for greater than 3 months

b. GFR greater than 60 mL/min per 1.73 m^2 accompanied by evidence of structural damage or other markers of functional kidney abnormalities

8. GFR calculations:

a. Children less than 18 years old- Creatinine Based "Bedside Schwartz" Equation:

GFR = 0.413 x (height in cm/serum creatinine)

b. Patients 18-25 years old- Creatinine Cystatin C (cysC) Based Chronic Kidney Disease in Children (CKID) equation:

Estimated GFR = 39.8 x [Height/Serum Creatinine]0.456 x [1.8/cysC]0.418 x [30/BUN]0.079 x [1.076male] [1.00female] x [Height/1.4]0.179

9. Organ dysfunction table per International pediatric sepsis consensus conference[7].

We will use the organ dysfunction table below per the International Pediatric Sepsis Consensus Conference to assess organ dysfunction and SIRS (Table 2) [7]. Any patients that meet criteria for organ dysfunction or SIRS will be exempt from the study except for patients with elevated bilirubin or liver enzymes (ALT or AST) as these may be elevated due to choledocholithiasis and other biliary pathology requiring ERCP intervention.

Cardiovascular dysfunction

Despite administration of isotonic intravenous fluid bolus ≥40 mL/kg in 1 hr

- Decrease in BP (hypotension) <5th percentile for age or systolic BP <2 SD below normal for age[a]

OR

- Need for vasoactive drug to maintain BP in normal range (dopamine >5 μg/kg/min or dobutamine, epinephrine, or norepinephrine at any dose)

OR

- Two of the following
  - Unexplained metabolic acidosis: base deficit >5.0 mEq/L
  - Increased arterial lactate >2 times upper limit of normal
  - Oliguria: urine output <0.5 mL/kg/hr
  - Prolonged capillary refill: >5 secs
  - Core to peripheral temperature gap >3°C

Respiratory[b]

- Pao_2/Fio_2 <300 in absence of cyanotic heart disease or preexisting lung disease

OR

- $Paco_2$ >65 torr or 20 mm Hg over baseline $Paco_2$

OR

- Proven need[c] or >50% Fio_2 to maintain saturation ≥92%

OR

- Need for nonelective invasive or noninvasive mechanical ventilation[d]

Neurologic

- Glasgow Coma Score ≤11 (57)

OR

- Acute change in mental status with a decrease in Glasgow Coma Score ≥3 points from abnormal baseline

Hematologic

- Platelet count <80,000/mm^3 or a decline of 50% in platelet count from highest value recorded over the past 3 days (for chronic hematology/oncology patients)

OR

- International normalized ratio >2

Renal

- Serum creatinine ≥2 times upper limit of normal for age or 2-fold increase in baseline creatinine

Hepatic

- Total bilirubin ≥4 mg/dL (not applicable for newborn)

OR

- ALT 2 times upper limit of normal for age

BP, blood pressure; ALT, alanine transaminase.

[a]See Table 2; [b]acute respiratory distress syndrome must include a Pao_2/Fio_2 ratio ≤200 mm Hg, bilateral infiltrates, acute onset, and no evidence of left heart failure (Refs. 58 and 59). Acute lung injury is defined identically except the Pao_2/Fio_2 ratio must be ≤300 mm Hg; [c]proven need assumes oxygen requirement was tested by decreasing flow with subsequent increase in flow if required; [d]in postoperative patients, this requirement can be met if the patient has developed an acute inflammatory or infectious process in the lungs that prevents him or her from being extubated.

2.0 Objectives

1. Evaluate the efficacy of IV Ketorolac and rectal Indomethacin in preventing PEP in patients undergoing ERCP.
2. To compare efficacy of IV ketorolac, as compared to rectal indomethacin, to reduce rates of PEP
3. To determine if the use of IV ketorolac, as compared to rectal indomethacin, reduces PEP sequelae
4. To identify possible biomarkers to predict PEP

2.1 Endpoints

1. Primary endpoint: Post-ERCP Pancreatitis (Time Frame: 2 weeks)
    a. Number of patient who develop PEP
2. Secondary endpoints:
    a. Increased pain after ERCP
    b. Next day post-ERCP pain score
    c. Laboratory markers associated PEP (Amylase and Lipase)
    d. Length of stay
    e. Severity of pancreatitis (mild, moderately severe, severe)
    f. Inflammatory markers
    g. Post-ERCP bleeding

3.0 Study Design

This will be a prospective study where patients will be randomized via a static sheet of randomization scheme into either rectal indomethacin (>=50 kg, 100 mg; 30-49 kg, 50 mg; 10-29 kg, 25 mg) or IV ketorolac 0.5 mg/kg (maximum: 15 mg).

After the procedure, patients will be started on D5 Lactated Ringers (D5LR) at 1.5 maintenance rate as per the ERCP order set and a clear liquid diet to be advanced as tolerated within 6 hours.

A minimum of 3 pain assessments are to be completed by nursing staff/anesthesia during admission:

Anesthesia/ PACU- initial pain assessment
Evening-2100- pain assessment by RN
Morning –0800- pain assessment by RN

If pain (worse than on admission) based on FLACC or NRS scoring or nausea occurs this will trigger a best practice order set for the primary provider to obtain a standard set of lab work. The lab work to be obtained is standard of care including: CRP, CBC w/ differential, Amylase, and Lipase. If patient meets criteria for PEP, they will remain on D5LR and diet to be returned to a clear liquid diet.

4.0 Study Procedures

Either medication will be administered upon endoscope insertion. For planned procedures, after consent is obtained patients will be directly placed into our static randomization sheet to determine which treatment arm he or she receives. This document will be available electronically to endoscopists, CRCs, and other pertinent team members via our medically secured REDCap database.

<u>Data Collection in REDCap:</u>

Data collected may include patient name, age, date of birth, sex, height, weight, relevant lab values, results of imaging modalities (MRCP, CT, US, or ERCP, EUS), genetic testing, family history, pancreatic function testing results (such as fecal fat, fecal elastase), medications, pain scores, hospital stay, complications, clinical course and progression, and interventions or surgical procedures. Relevant data from any Cincinnati Children's Hospital Medical Center (CCHMC) admission or clinic visit may be utilized. Data will be collected on specific case report forms (CRFs) that will be entered into a Research Electronic Data Capture (REDCap) database. REDCap is a CTSA sponsored, widely used, secure, web-based application designed for data management. REDCap satisfies all good clinical practices guidelines. Each participant will be identified with a study ID number, and the key will be maintained in a separate password protected file. Only authorized study personnel will have access to this key. Computer files will also be password protected and data will be entered into the secure web-based database.

Specimen Collection:
Optional blood specimens for this study will be obtained for research purposes only.
When possible we will obtain research blood at the time of a clinical blood draw or when a patient is anesthetized for a procedure. Blood collection for this protocol will follow the blood collection guidelines for children - the lesser of 3 ml/kg of blood or a maximum of 10 ml per sample will be collected for research purposes. A single blood draw will not exceed 3 ml/kg, and no more than 4 ml/kg (5% of total blood volume) will be drawn over a one month period. This protocol allows for up to three blood samples per ERCP-related appointment or admission for up to 24 months following enrollment.

Repeat ERCPs:
Some subjects will have more than one clinically indicated ERCP. Subjects will be eligible for randomization of IV ketorolac versus rectal indomethacin for each clinically indicated ERCP for the duration of the study.

5.0 Subject Population

The subject population will include patients 6 months to 21 years of age requiring ERCP. This pediatric population has not yet been evaluated in a randomized trial to compare IV ketorolac versus rectal indomethacin for PEP prophylaxis; both treatments are current standard of care for acute pancreatitis.

Inclusion criteria-

- Any patient undergoing ERCP (diagnostic or therapeutic with cannulation of the major or minor papilla)
- Age 6 month- 21 years old
- Does not meet exclusion criteria

Exclusion criteria-

- < 10 kg
- Low risk subgroup: Biliary indication with history of prior biliary sphincterotomy.
- High risk for bleeding (Example: Planned liver biopsy)
- Gastrointestinal bleeding in previous 3 days
- Acute pancreatitis (within 3 days) at the time of ERCP
- Use of NSAIDs in the previous 5 days
- Peptic ulcer disease
- Acute kidney Injury or Known Chronic Kidney Disease per KDIGO

- Pregnancy (Pregnancy tests are administered prior to ERCP as standard of care)
- Lithium therapy
- Allergy to ketorolac or indomethacin
- Organ Dysfunction or SIRS

6.0 Selection and Recruitment of Study Participants

Subject Recruitment:

Recruited subjects will be identified through review of patients presenting for ERCP for clinical care. Following screening, patients will be enrolled by the research staff after informed consent is obtained through the informed consent process mentioned below.

Process of obtaining Consent (including eConsent):

Consent, parental permission and/or assent will be obtained from all patients before any study-related procedures are performed. Written assent will be obtained from participants 11 years of age and older. The investigator will be available to answer any questions that the participant or parent may have regarding procedures, risks, and alternatives. The consent process will be documented on the informed consent process note.

Consent may take place by several methods: in-person paper consent, in-person electronic consent (using REDCap for the eConsent) or over the phone (via paper or REDCap for eConsent). Signatures of the subject and study staff may not always occur on the same date depending on how and when the subject returns the signed consent. No matter the consenting process, study procedures will not occur prior to a fully executed consent form. Consent will be obtained following the CCHMC consenting SOP. REDCap eConsent will not replace the consenting method, it will be used as an additional resource for signing the consent form. A copy of the consent form will either be given to the subject in paper form or emailed to them via REDCap depending on how the consent is completed. In all cases, the consent process will be documented on the informed consent process note and a copy of the signed consent(s) will be kept in the patient's medical record.

Staff will make sure that the eConsent database is updated as soon as possible after a new version of the paper consent is approved. Staff will also make sure paper consents are used to consent eligible subjects in the event that the eConsent database is not updated prior to eligible subjects being available for consent approach by a member of the study staff. For the reasons described, the eConsent will not be submitted to the IRB for approval.

Subjects will be reminded that participation in research is completely voluntary. Coercion is eliminated by having the subjects sign an assent document and the parent/guardian signs the consent document. We will give potential subjects time to read the consent form, consent them in a private setting, and answer any questions they may have. Potential subjects (or parents) will be told that the subject's (parent's) decision to participate will not affect the clinical care received.

Subjects will be informed that signing the informed consent form will provide consent for randomization to receive Rectal Indomethacin or IV Ketorolac for all repeat ERCP procedures. Re-consent will not be required at each procedure. However, the family will be reminded of their participation prior to any future procedures and be given the opportunity to opt out if requested.

If patients do not want to participate, at any time, they are instructed to call the Research Coordinator to opt out. The study consent process will ensure that potential subjects will be adequately informed about the study and will have an opportunity to ask questions.

7.0 Data Management & Analysis

1. Data will be stored in REDCap. Study data will be restricted to study personnel only after all research training is complete.
2. Once data is collected, a code will be created. The identifying information will be removed from the data file and replaced with the code. Codes will be stored in a separate file. Only research personnel will have access to the data.
3. Research blood samples (stored for extraction of plasma and DNA) will be obtained and banked during the subject's ERCP. All samples will be collected and processed from specimen tubes containing the subject's unique study identification code. Specimens will be stored in the Pancreatitis Registry biorepository (IRB 2012-4050) identified only by their study ID code. The password protected bio-specimen database which associates unique study codes with personal identifiers will be accessible only to essential staff members designated by the PI. Leftover specimens will be banked for future IRB approved research.
4. Once the study is complete, data will be retained in a coded state for potential future currently unspecified research. Future research will require IRB approval prior to utilizing this dataset.

7.1 Statistical Analysis Plan

Descriptive analysis of the data using means ± standard deviations, medians and interquartile ranges (25th-75th percentiles), ranges, confidence intervals, proportions and frequencies will be performed. We will examine the distribution of all variables to identify outliers and if continuous variables are normally distributed or skewed. Additional statistical analysis of the data may include t-tests or Mann-Whitney Wilcoxon tests, Chi-square or Fischer's exact tests, ANOVA, and/or regressions to test for differences in those developing PEP between the medication groups as well as identify risk factors for developing PEP. We will control for confounders of therapy by standardizing time of medications intra-operatively, the type and rate of IV fluids, and advancement of diet through our ERCP order set. Statistical analyses will be performed using SAS®, version 9.4 (SAS Institute, Cary, North Carolina, USA). A p-value <0.05 will be considered statistically significant. Two-sided tests will be used for group comparisons in order to assess any differences between the medication groups. If one medication has a significantly ($p<0.05$) lower proportion of PEP and significantly decreased odds ratio of developing PEP then that medication would be deemed preferable over the other after assessing and controlling for any confounding factors.

Multiple samplings of the same patient would be important for potential drug-drug comparison as well as the overall proportion of PEP for generalizability purposes in order to have the most procedures/data for this study. We will report on the number of patients that had single and multiple procedures. In order to address the multiple sampling from the same participant issue (to avoid overweighting certain patients that could influence the results) we will do a sensitivity analysis and use the first procedure for each patient and compare the outcomes of the single procedures to the overall outcomes in order to make sure the findings are consistent. If there would be any differences in results or conclusions drawn using the first procedure vs overall data, we will report on these differences and then use the first procedure performed.

Per internal power calculation for 80% power the study will require 96 patients in each treatment group (96 IV ketorolac and 96 rectal indomethacin) - 192 patients total. For 90% power, would need 128 patients in each treatment group (128 IV ketorolac, 128 rectal indomethacin) - 256 total patients.

8.0 Potential Risks and Benefits to Subjects

8.1 Potential Risks

The level of risk for the participants is minimal. Both indomethacin and ketorolac are standard of care treatments. However, the risks associated with each medication are listed below:

Ketorolac adverse reactions: Abdominal pain, dyspepsia, and nausea (>10%); increased liver enzymes (≤ 15%), and headache (>10%). All other adverse reactions are less than 10%.

Indomethacin adverse reactions: Vomiting (≤ 12%), postoperative hemorrhage (≤ 11%), and headache (12-16%). All other adverse reactions are less than 10%.

Risks associated with a breach of confidentiality: There is a risk that someone not authorized to view participant information, including identifiable information, will gain access to this information. We will take measures to prevent this from happening and will comply with local regulations. To protect patient information, research records and source documents will be maintained in a research file and stored in the investigators locked office or in password protected electronic files. No primary data or patient identifiers will be published.

8.2 Data Safety Monitoring Plan:

This study is a minimal risk study. Therefore, no formal data safety monitoring board will be appointed. Adverse events related to the study procedures will be monitored by the study coordinator and reported to the PI. The PI will then report any adverse events in writing to the CCHMC IRB within the time frame specified in the IRB guidelines. These procedures should be highly effective in minimizing risk to study participants.

8.3 Potential Benefits:

There is no direct benefit to the study subject. However, future patients may benefit due to the knowledge gained from this study that may direct future patient care.

8.4 Privacy & Confidentiality:

Access to original data and study materials will be limited to the investigative team. Every effort will be made to protect each research participant's identity. Each participant will be identified with a study ID number, and the key will be maintained in a password protected file. Only authorized site personnel will have access to this key. Computer files will also be password protected.

Research subjects will be informed that agencies that make rules and policies about how research is done have the right to review these records, as well as agencies that pay for the study. Only study staff, Institutional Review Board, OHRP, and NIH representatives will have access to study records.

9. 0 Timeline/ Budget

Study recruitment will begin at CCHMC in October 2022. Per internal power calculation for 80% power the study will require 96 patients in each treatment group (96 IV ketorolac and 96 rectal indomethacin) - 192 patients total. For 90% power, it would require 128 patients in each treatment group (128 IV ketorolac, 128 rectal indomethacin) - 256 total patients. We hope to enroll 96 patients in each treatment arm to reach 80% power for the study.

At our tertiary care center, 180 to 190 ERCP cases are completed per year. We should be able to complete recruitment by spring 2024, although we may need to extend the recruitment period to acquire sufficient power to complete the study. We anticipate data analysis to be completed in the spring to summer of 2024.

We anticipate that the cost will be minimal, as the labs will be standard of care. All treatment charges will be billed to the patient and/or the patient's insurance company because they are the standard of care for acute pancreatitis. We will have access to a modest amount of funding via the NIH T32 training grant to cover any ancillary costs of the study. Any labs that are not obtained by the primary team, will be obtained at the research cost and will be entered into research EPIC. The patients will be entered into EPIC as a mixed inpatient/research encounter.

10.0 Bibliography:

1. Mark, J.A. and R.E. Kramer, *Ketorolac Is Safe and Associated With Lower Rate of Post-Endoscopic Retrograde Cholangiopancreatography Pancreatitis in Children With Pancreatic Duct Manipulation.* J Pediatr Gastroenterol Nutr, 2021. **73**(4): p. 542-547.
2. Geraci, G., et al., *Rectal Diclofenac administration for prevention of post-Endoscopic Retrograde Cholangio-Pancreatography (ERCP) acute pancreatitis. Randomized prospective study.* Clin Ter, 2019. **170**(5): p. e332-e336.
3. Abu-El-Haija, M., et al., *Classification of Acute Pancreatitis in the Pediatric Population: Clinical Report From the NASPGHAN Pancreas Committee.* J Pediatr Gastroenterol Nutr, 2017. **64**(6): p. 984-990.
4. Committee, A.S.o.P., et al., *Complications of ERCP.* Gastrointest Endosc, 2012. **75**(3): p. 467-73.
5. Merkel, S.I., et al., *The FLACC: a behavioral scale for scoring postoperative pain in young children.* Pediatr Nurs, 1997. **23**(3): p. 293-7.
6. Ferreira-Valente, M.A., J.L. Pais-Ribeiro, and M.P. Jensen, *Validity of four pain intensity rating scales.* Pain, 2011. **152**(10): p. 2399-2404.
7. Goldstein, B., et al., *International pediatric sepsis consensus conference: definitions for sepsis and organ dysfunction in pediatrics.* Pediatr Crit Care Med, 2005. **6**(1): p. 2-8.