The Safety of Ketorolac in Surgical Neonates

IND Number: In progress

Principal Investigator: Jennifer H. Aldrink, MD

Version 5.0
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STATEMENT OF COMPLIANCE

The study will be carried out in accordance with Good Clinical Practice (GCP) as required by the following:

- United States (US) Code of Federal Regulations (CFR) applicable to clinical studies (45 CFR Part 46; 21 CFR Part 50, 21 CFR Part 56, and 21 CFR Part 312)
- ICH regulations
- Institutional and IRB policies and guidelines
- Terms of Award

All key personnel (all individuals responsible for the design and conduct of this study) have completed Human Subjects Protection Training.

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LIST OF ABBREVIATIONS

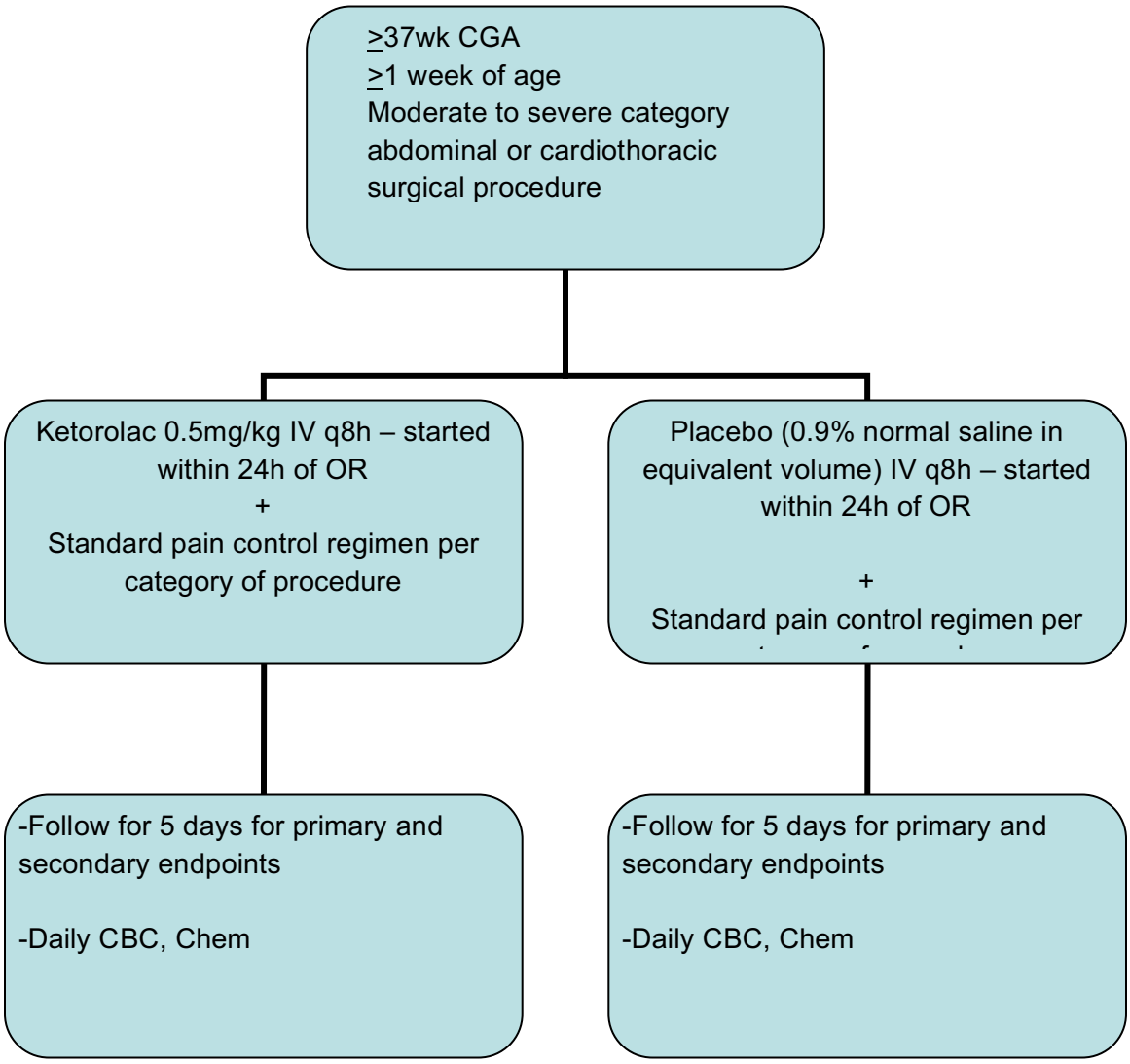
AE	Adverse Event/Adverse Experience
CFR	Code of Federal Regulations
CIOMS	Council for International Organizations of Medical Sciences
CONSORT	Consolidated Standards of Reporting Trials
CFR	Code of Federal Regulations
CRF	Case Report Form
CRO	Contract Research Organization
DCC	Data Coordinating Center
DHHS	Department of Health and Human Services
DMID	Division of Microbiology and Infectious Diseases, NIAID, NIH, DHHS
DSMB	Data and Safety Monitoring Board
eCRF	Electronic Case Report Form
FDA	Food and Drug Administration
FWA	Federalwide Assurance
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
ICMJE	International Committee of Medical Journal Editors
IDE	Investigational Device Exemption
IEC	Independent or Institutional Ethics Committee
IND	Investigational New Drug Application
IRB	Institutional Review Board
ISM	Independent Safety Monitor
JAMA	Journal of the American Medical Association
MedDRA ®	Medical Dictionary for Regulatory Activities
MOP	Manual of Procedures
N	Number (typically refers to subjects)
NCI	National Cancer Institute, NIH, DHHS
NDA	New Drug Application
NEJM	New England Journal of Medicine
NIAID	National Institute of Allergy and Infectious Diseases, NIH, DHHS
NIH	National Institutes of Health
OCRA	Office of Clinical Research Affairs, DMID, NIAID, NIH, DHHS
OHRP	Office for Human Research Protections
OHSR	Office for Human Subjects Research
ORA	Office of Regulatory Affairs, DMID, NIAID, NIH, DHHS

PHI	Protected Health Information
PI	Principal Investigator
PK	Pharmacokinetics
QA	Quality Assurance
QC	Quality Control
SAE	Serious Adverse Event/Serious Adverse Experience
SMC	Safety Monitoring Committee
SOP	Standard Operating Procedure
US	United States
WHO	World Health Organization

PROTOCOL SUMMARY

Title:	**The Safety of Ketorolac in Surgical Neonates**
Phase:	**II**
Population:	**Neonates aged 1week to 3 months who undergo an abdominal, cardiac, or thoracic surgical procedure at Nationwide Children's Hospital, Columbus, Ohio. Sample size will include 60 patients.**
Number of Sites:	**Nationwide Children's Hospital, Columbus, Ohio**
Study Duration:	**1-2 years**
Subject Participation Duration:	**Five days**
Description of Agent or Intervention:	**Ketorolac 0.5mg/kg (or placebo, 0.9% normal saline) intravenous every 8 hrs for 72hrs. First dose administered within 24hrs following the completion of the surgical procedure.**
Objectives:	**Primary:** The primary purpose of this study is to compare bleeding events in neonates who receive ketorolac and those who do not receive ketorolac. We hypothesize that ketorolac is safe and effective in infants $\geq$ 37wks corrected gestational age and at least one week of age. **Secondary:** We intend to evaluate daily creatinine levels, pain scores, urine output per shift, platelet counts, hemoglobin levels, number of days on the ventilator, amount of opioid administered, blood pressure, and reintubation events on all patients in this study as secondary study points.
Description of Study Design:	**See schematic below**
Estimated Time to Complete Enrollment:	**1-2 years**

***Schematic of Study Design**:



1 KEY ROLES

Individuals:

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2 BACKGROUND INFORMATION AND SCIENTIFIC RATIONALE

2.1 Background Information

Ketorolac is a nonsteroidal anti-inflammatory agent that has been demonstrated to be an effective drug in relieving moderate to severe postoperative pain in adults and children.1-5 Ketorolac can reduce the opioid requirements following surgery, and may therefore prevent some of the opioid-induced undesirable adverse effects, including respiratory depression, central nervous system disturbances, urinary retention, and prolonged ileus. However, ketorolac carries its own risks of increased bleeding complications and renal insufficiency. Ketorolac's mechanism of action is as a reversible inhibitor of cyclooxygenase-1 and -2 (COX-1 and COX-2) enzymes, which results in the decreased formation of prostaglandin precursors. This has some effect on renal perfusion. In addition, given its effects on platelet adhesion and aggregation, it may prolong bleeding time. Ketorolac is renally cleared, and in patients with renal dysfunction, its clearance may be prolonged.

Neonates and young infants can be particularly challenging in the postoperative setting given legitimate concerns of respiratory depression following opioid administration.1 However, minimal safety or efficacy data on ketorolac currently exists in this age group in whom this drug could be a potentially useful adjuvant to opioids. The purpose of this study is to characterize the safety profile of ketorolac in infants age 0-3 months.

Papacci et al previously reported 18 neonates to whom ketorolac was administered in a postoperative or postprocedural setting, reporting it to be safe and efficacious in this population.(6) Others have studied these risks and complications of ketorolac in children and older infants. In a single center, prospective randomized controlled trial, Gupta et al evaluated the risk of bleeding complications related to ketorolac use for the treatment of postoperative pain in 75 infants and children undergoing congenital heart surgery.7 The median age of patients in this study was 10 months (range 2.5-174 months). Postoperative pain control consisted of ketorolac with opioid analgesics in one study arm, and opioid analgesics alone in the other study arm. The main outcome measured was bleeding complications as measured by chest-tube drainage, wound, and gastrointestinal bleeding. They demonstrated no significant differences between the two treatment arms with respect to any of these parameters, concluding ketorolac to be a safe and effective choice of alternate analgesia in treating postoperative pain in older infants and children undergoing congenital heart surgery.7

A paucity of data exists regarding its use in neonates and young infants less than 3 months of age. One retrospective review of 53 patients <6 months of age who received postoperative ketorolac following cardiac surgery also included 11 patients who were <1 month of age.8 This review found an increase in blood urea nitrogen/serum creatinine (SCr) levels from baseline following the administration of ketorolac, although the levels remained within normal limits during the course of therapy. Four patients (7.5%) had minor bleeding episodes, none of

which resulted in significant changes in hemoglobin or platelet levels, or required the transfusion of blood products. A smaller, retrospective review of 10 infants less than 6 months of age also demonstrated that ketorolac reduces the opioid requirement following abdominal surgery and can be administered safely to infants of 37 weeks CGA or greater.1 And Papacci's study reviewed the use of ketorolac in a neonatal setting in 18 infants whose average CGA was 37 +/- 4 weeks (range 25-38 weeks), and found no significant changes in hematological, renal, or hepatic parameters, and no resultant bleeding complications.6 While these conclusions appear promising for this very young age group, the numbers are quite small.

2.2 Rationale: This is the first study of which we know to evaluate the use of ketorolac exclusively in this neonatal age group. This study will help to define the safety of the drug and its potential for adjuvant pain control in this age group. We hypothesize that ketorolac is safe and effective in infants $\geq$ 37wks corrected gestational age and at least one week of age.

2.3 Potential Risks and Benefits

2.3.1 Potential Risks

Risks of ketorolac include the potential for bleeding events (1-3% in population), the risk of renal insufficiency (1-3% in population), and the risk of hypersensitivity reactions. These are accepted risks when using ketorolac in older infants, children, and adults. While these risks are small, the seriousness of such risks may be much greater and may involve the need for blood transfusions, additional procedures and/or reoperations, or additional laboratory or radiological studies.

Bleeding episodes will be defined by following:

1. Persistent bloody drainage from a nasogastric tube, resulting in a drop of hemoglobin of greater than or equal to 2g/dL (change of 1g/dL in hemoglobin may be explained by the infusion of perioperative crystalloid, and inthe abscence of hemodynamic instability would be considered within the acceptable standard deviation)

2. Surgical site bleeding resulting in a drop of hgb >2g/dL from inital postop value, unless the patient has required crystalloid or fluid boluses other than PRBC totalling 60ml/kg or greater.

3. Any hemodynamic instability associated with a drop of hemoglobin >2g/dL

Several published criteria for adults and children exist to enable the practitioner to identify early signs of renal injury (9-11). Of these, the Pediatric modification of the Risk, Injury, Failure, Loss, End-Stage Renal Disease (p-RIFLE) criteria are probably the most reliable in this population, as this has been validated in children.

2.3.2 Known Potential Benefits

Potential benefits include less postoperative pain, need for less opioid which potentially may lead to fewer days on the ventilator, faster return of bowel function, and shorter hospital stay.

3 OBJECTIVES

3.1 Study Objectives

The general purpose of this study is to characterize the safety profile of ketorolac in infants age 0-3 months. During the study, data will also be collected evaluating the change in the need for opioids in patients who receive ketorolac versus those who receive placebo.

Ketorolac 0.5mg/kg intravenously every 8 hrs for 72hrs will be administered versus an equivalent volume of 0.9% normal saline as placebo.

3.2 Study Outcome Measures

3.2.1 Primary Outcome Measures

Primary: The primary purpose of this study is to compare bleeding events in neonates who receive ketorolac and those who do not receive ketorolac. We hypothesize that ketorolac is safe and effective in infants $\geq$ 37wks corrected gestational age and at least one week of age. Primary outcomes measured include bleeding events and renal injury.

3.2.2 Secondary Outcome Measures

Secondary: We intend to evaluate daily creatinine levels, pain scores, urine output per shift, platelet counts, hemoglobin levels, number of days on the ventilator, amount of opioid administered, blood pressure, and reintubation events on all patients in this study as secondary study points.

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4 STUDY DESIGN

This is a Phase II, single center, randomized controlled pilot study. Hospitalized patients one week of age to 3 months of age who undergo an abdominal or thoracic surgical procedure within the moderate or severe degree of pain category (see attached Table 1: postoperative pain categories) will be randomized to receive standard pain management regimens plus placebo (0.9% saline of equivalent volume) or ketorolac 0.5mg IV q8h x 72h plus standard pain management regimens. The postoperative management will be unchanged and at the discretion of the attending surgeon, as appropriate for the surgical procedure. The patients will be followed for 5 days, or 48hrs from the end of ketorolac therapy for primary and secondary endpoints. Ketorolac will be started within 24hrs of the end of the operative procedure.

5 STUDY ENROLLMENT AND WITHDRAWAL

Annually, we see approximately 80 -100 patients who would be potential candidates for this study. The proposed sample size for this study is 50 patients, 25 in each group. We anticipate the time to completion of this study will be 1-2 years. The duration of subject participation will be 5 days. The parents or guardians of potential patients will be approached preoperatively by the study personnel for explanation of the study, its purpose, risks, and potential benefits. Consent will be obtained by one of the investigators of the study.

5.1 Subject Inclusion Criteria

1. Infants gestational age ≥37 weeks corrected gestational age and greater than or equal to one week of age to 3 months of age
2. Infants who are undergoing a surgical procedure on the abdomen or chest (cardiothoracic)
3. The parent or guardian has given informed consent.

5.2 Subject Exclusion Criteria

1. Gestational age <37 weeks
2. Age less than one week or greater than 3 months of age
3. Known renal disease/dysplastic kidneys
4. Serum Creatinine >0.4
5. Patients who have rising creatinine levels the day prior to surgery (increase of at least 1.5-fold from baseline)
6. Patients who are currently receiving other potentially renal toxic drugs or drugs that may interfere with hemostatic pathways as part of their clinical care (including but not limited to hydrochlorothiazide, vancomycin, gentamicin, aspirin, TPA [except for use of thrombosed central venous catheters], enalapril, systemic heparin [except for use in central venous catheter flushes])
    a. Furosemide will be allowable as is relevant particularly to postoperative cardiothoracic patients. UOP must be >1ml/kg/h while on receiving furosemide and study drug/placebo, and the patient will be under the constant supervision of a physician assessing patient perfusion
7. Patients who undergo nephrectomy
8. Patients with necrotizing enterocolitis
9. Patients with a hemoglobin value <9g/dL
10. Recent (within 3 months) GI bleeding, ulceration, and/or perforation
11. Platelet count < 50,000
12. Ongoing disseminated intravascular coagulation or history of intraventricular hemorrhage
13. Recent use or current use of other nonsteroidal anti-inflammatory drugs (NSAIDS) besides aspirin (ASA)
14. Allergy to ASA or other NSAIDS

5.3 Treatment Assignment Procedures

5.3.1 Randomization Procedures

This trial is randomized. Patients will be randomized according to a fixed 1:1 allocation. The overall sample size will be 50 patients, 25 in each group. The randomization scheme will consist of a permuted block randomization in which the blocking factor varies randomly between 4 and 6.

Randomization will be stratified by pain category (moderate and severe, refer to pain management guidelines).

An observational arm was added for those patients who do not wish to be randomized. If consent is obtained for this arm of the study, then study staff will be allowed to follow and record clinical data as applicable and stated for this study. Patients will receive postoperative pain control as per the discretion of their primary provider.

5.3.2 Masking Procedures

The randomization strategy will be performed by an independent person to ensure investigator masking to the process.

5.3.3 Reasons for Withdrawal

Those who will monitor the data include the study staff physicians and pharmacist. The data to be monitored include any bleeding events, evaluation of renal function including BUN and Creatinine levels. These will be monitored on an individual patient basis at least daily. Additional outcomes as mentioned in primary and secondary outcomes section will be monitored.

Bleeding events: Bleeding events will be closely monitored in the NICU setting. Daily CBC's are obtained during the postoperative period, and these will be recorded as data relevant to the study. Deviations in hemoglobin or platelet counts will be detected, and treated as is standard of care.

Bleeding episodes will be defined by following:

1. Persistent bloody drainage from a nasogastric tube, resulting in a drop of hemoglobin of greater than or equal to 2g/dL (change of 1g/dL in hemoglobin may be explained by the infusion of perioperative crystalloid, and in the absence of hemodynamic instability would be considered within the acceptable standard deviation)

2. Surgical site bleeding resulting in a drop of hgb >2g/dL from initial postop value, unless the patient has required crystalloid or fluid boluses other than PRBC totalling 60ml/kg or greater.

3. Any hemodynamic instability associated with a drop of hemoglobin >2g/dL

Renal injury: Several published criteria for adults and children exist to enable the practitioner to identify early signs of renal injury (9-11). Of these, the Pediatric modification of the Risk, Injury, Failure, Loss, End-Stage Renal Disease (p-RIFLE) criteria are probably the most reliable in this population, as this has been validated in children.

Based upon these criteria, renal function will be monitored frequently. Based upon the following criteria, a patient will be unblinded and pulled from the study:

1. Patients who are resuscitated but with continued postoperative UOP<0.5ml/kg/h persistent over 8 hours

2. A decrease in estimated creatinine clearance by 25%, in a well-resuscitated patient

5.3.4 Withdrawals

Subjects are free to withdraw from participating in the study at any time upon request.

The patient will become unblinded and pulled from receiving the study drug or placebo if any bleeding events occur or if renal function worsens (rise in greater than 0.5mg/dL). However, events will still be recorded on the patient, and these patients will still be followed for the duration of the study (i.e. 5 days or 72 hrs from the end of the study drug), or until resolution and or through treatment of an adverse event.

In addition, an evaluation and possibly a change in the study protocol will be initiated due to safety concerns.

6 STUDY INTERVENTION/INVESTIGATIONAL PRODUCT

6.1 Study Product Description

Ketorolac tromethamine is a member of the pyrrolo-pyrrole group of nonsteroidal anti-inflammatory drugs (NSAIDs) and supplied as a racemic mixture of [-]S and [+]R ketorolac tromethamine. Ketorolac tromethamine may exist in three crystal forms; all forms are equally soluble in water. Ketorolac tromethamine has a pKa of 3.5 and an n-octanol/water partition coefficient of 0.26. The molecular weight of ketorolac tromethamine is 376.41 and the molecular formula is $C_{19}H_{24}N_2O_6$.

6.1.1 Acquisition

Ketorolac tromethamine will be obtained by the pharmacy department from Hospira, Inc.

6.1.2 Formulation, Packaging, and Labeling

Ketorolac tromethamine is supplied as a 30mg/mL clear to slightly yellow sterile solution for injection in a 1mL single-dose vial. The solution contains 10% (w/v) alcohol.

6.1.3 Product Storage and Stability

Ketorolac tromethamine will be stored at room temperature (20-25 degrees Celsius) in its original container and protected from light. The product will be maintained securely by the pharmacy department and stored separately from the general stock.

6.2 Dosage, Preparation and Administration of Study Intervention/Investigational Product

Dosage

The dose of ketorolac is 0.5mg/kg given intravenously every 8 hours for 72 hours. The first dose will be given within 24hrs from the conclusion of the surgical procedure. A total of 9 doses will be administered.

Preparation & Blinding

Subjects will be assigned to treatment or placebo in sequential order as indicated by the provided randomization scheme. The pharmacy will then aseptically prepare the blinded syringe of investigational product. Ketorolac will be diluted with 0.9% Sodium Chloride to a

concentration of 0.6mg/mL. Subjects assigned to placebo will be given 0.9% Sodium Chloride at a volume equivalent to the active product.

All study syringes will be administered within 24 hours of preparation.

6.3 Modification of Study Intervention/Investigational Product for a Participant

Dose modifications will not be performed, as this drug will be administered on a weight-based calculation. Patients who experience a bleeding episode or acute change in renal function as defined previously (Section 5.2.3) will not have dose modification, but will be pulled from the study.

6.4 Accountability Procedures for the Study Intervention/Investigational Product(s)

All investigational products will be maintained by the pharmacy department and stored separately from the general stock. Upon receipt of the product, an inventory will be performed and contents of the shipment verified. Accountability logs will be maintained by the pharmacy and indicate all investigational product that has been received, dispensed, and destroyed at the site.

6.5 Concomitant Medications/Treatments

All current medications and therapies will be continued during this study with the exception of those listed in the exclusion criteria.

7 STUDY SCHEDULE

7.1 Study Evaluations

Written informed consent will be obtained from the eligible patient's parent or guardian prior to their operative procedure. Consent will be obtained from one of the investigators listed on the study protocol.

Eligible subjects will be randomized to receive standard pain management regimens plus placebo (0.9% saline of equivalent volume) or ketorolac 0.5mg IV q8h x 72h plus standard pain management regimens, post-operatively. The study drug will be started within 24hrs of the operative procedure.

All subjects will undergo daily physical examinations by their operating surgeon and team (including nurse practitioners, surgical residents, surgical fellows, nursing staff). Days on the ventilator, reintubation events, blood urea nitrogen levels, creatinine levels, neonatal pain scores (NPASS), urine output per shift, platelet values, hemoglobin values, blood pressure, amount of opioid used, other medications patient is receiving, intraoperative issue/complications will be recorded.

Patients will have daily laboratory tests including complete blood counts and chemistry panels as would be routine for their postoperative care.

The following laboratory evaluations will be performed daily on patients enrolled in this study, as part of their routine postoperative care. Additional laboratory studies may be obtained as indicated by the patient's condition. Laboratory specimens will be obtained via heelstick, arterial line (if existent), or central venous catheter (if existent). Specimen volumes will be minimalized to 0.5ml per tube.

Hematology: hemoglobin, hematocrit, white blood cells (WBC) with differential count, platelet count.

Biochemistry: blood urea nitrogen, creatinine, electrolytes.

Coagulation profile: protime, prothrombin time, INR

No additional testing will be required by the study, unless signs of renal injury or bleeding events occur.

7.2 Follow-up

The drug/placebo will be administered every 8 hours for 72 hours, unless the medication is stopped earlier due to an AE. Patients will be followed for 48 hours from the completion of the drug/placebo administration. After 48 hours, the study will be concluded for that patient. There will be no further follow-up evaluations or visits.

8 STUDY PROCEDURES/EVALUATIONS

8.1 Specification of Safety Parameters

Events will be collected during the duration of the study, which is 48 hours from the completion of the study drug/placebo.

Bleeding episodes will be defined by following:

- Persistent bloody drainage from a nasogastric tube, resulting in a drop of hemoglobin of greater than or equal to 2g/dL (change of 1g/dL in hemoglobin may be explained by the infusion of perioperative crystalloid, and in the absence of hemodynamic instability would be considered within the acceptable standard deviation)
- Surgical site bleeding resulting in a drop of hemoglobin >2g/dL from initial postop value, unless the patient has required crystalloid or fluid boluses other than PRBC totalling 60ml/kg or greater.
- Any hemodynamic instability associated with a drop of hemoglobin >2g/dL

2. Renal injury will be defined by the following:

- Patients who are resuscitated but with continued postoperative UOP<0.5ml/kg/h persistent over 8 hours
- A decrease in estimated creatinine clearance by 25%, in a well-resuscitated patient

8.2 Methods and Timing for Assessing, Recording, and Analyzing Safety Parameters

8.2.1 Adverse Events

Adverse Event: ICH E6 defines an AE as any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product regardless of its causal relationship to the study treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of medicinal (investigational) product. The occurrence of an AE may come to the attention of study personnel during study visits and interviews of a study recipient presenting for medical care, or upon review by a study monitor.

All AEs including local and systemic reactions not meeting the criteria for "serious adverse events" should be captured on the appropriate CRF. Information to be collected includes event description, time of onset, clinician's assessment of severity, relationship to study product (assessed only by those with the training and authority to make a diagnosis, which would include MD, PA, Nurse Practitioner, DO, or DDS), and time of resolution/stabilization of the event. All AEs occurring while on study must

be documented appropriately regardless of relationship. All AEs will be followed to adequate resolution.

Any medical condition that is present at the time that the patient is screened should be considered as baseline and not reported as an AE. However, if it deteriorates at any time during the study, it should be recorded as an AE.

All AEs must be graded for severity and relationship to study product.

Severity of Event: All AEs will be assessed by the clinician using a protocol defined grading system. For events not included in the protocol defined grading system, than the following guidelines will be used to quantify intensity.

Mild: events require minimal or no treatment and do not interfere with the patient's daily activities.

Moderate: events result in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with functioning.

Severe: events interrupt a patient's usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually incapacitating.

Life threatening: any adverse drug experience that places the patient or subject, in the view of the investigator, at immediate risk of death from the reaction as it occurred, ie, it does not include a reaction that had it occurred in a more severe form, might have caused death.

Changes in the severity of an AE should be documented to allow an assessment of the duration of the event at each level of intensity to be performed. Adverse events characterized as intermittent require documentation of onset and duration of each episode.

Relationship to Study Products: The clinician's assessment of an AE's relationship to test article (vaccine or study drug) is part of the documentation process, but it is not a factor in determining what is or is not reported in the study. If there is any doubt as to whether a clinical observation is an AE, the event should be reported. All AEs must have their relationship to study product assessed using the terms: associated or not associated. In a clinical trial, the study product must always be suspect. To help assess, the following guidelines are used.

- Associated – The event is temporally related to the administration of the study product and no other etiology explains the event.
- Not Associated – The event is temporally independent of study product and/or the event appears to be explained by another etiology.

8.2.2 Serious Adverse Events

Serious Adverse Event (SAE): An SAE is defined as an AE that meets one of the following conditions:

Death during the period of protocol defined surveillance

Life-threatening event (defined as a subject at immediate risk of death at the time of the event)

An event requiring inpatient hospitalization or prolongation of existing hospitalization during the period of protocol defined surveillance

Results in a persistent or significant disability/incapacity

Any other important medical event that may not result in death, be life threatening, or require hospitalization, may be considered a serious adverse experience when, based upon appropriate medical judgment, the event may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed above. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

All SAEs will be:

- recorded on the appropriate SAE source document
- followed through resolution by a study clinician
- reviewed and evaluated by a study clinician

8.2.3 Procedures to be followed in the Event of Abnormal Laboratory Test Values or Abnormal Clinical Findings

Bleeding will be closely monitored in the NICU setting. Daily CBC's are obtained during the postoperative period, and these will be recorded as data relevant to the study. Deviations in hemoglobin or platelet counts will be detected, and treated as is standard of care. If concern arises about the drug, the patient will be unblinded and pulled from receiving the study drug or placebo. However, events will still be recorded on the patient. Collection of laboratory data should be limited to those laboratory parameters that are relevant to safety, study outcome measures, and/or clinical outcome.

8.3 Reporting Procedures

8.3.1 Regulatory Reporting for Studies Conducted Under a Sponsor-Investigator IND

Following notification to the investigator, the Sponsor Investigator, will report events that are both serious and unexpected and that are associated with study product(s) to the Food and Drug Administration (FDA) within the required timelines as specified in 21 CFR Part 312.32: fatal and life-threatening events within 7 calendar days (by phone or fax) and all other SAEs in writing within 15 calendar days. All serious events designed as “not associated” to study product(s), will be reported to the FDA at least annually in a summary format.

9 CLINICAL MONITORING

Site monitoring is not applicable for this single center pilot study.

10 STATISTICAL CONSIDERATIONS

10.1 Study Hypotheses

We hypothesize that ketorolac is safe and effective in infants ≥ 37wks corrected gestational age and at least one week of age.

10.2 Sample Size Considerations

This is a pilot study for safety. There are no statistical considerations for these small numbers. This study will hopefully provide some background data for a large scale, multi-center study with statistical significance.

11 ETHICS/PROTECTION OF HUMAN SUBJECTS

11.1 Ethical Standard

The investigator will ensure that this study is conducted in full conformity with the principles set forth in The Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research of the US National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research (April 18, 1979) and codified in 45 CFR Part 46 and/or the ICH E6; 62 Federal Regulations 25691 (1997).

11.2 Institutional Review Board

The study protocol and consent forms and any other related documents will undergo IRB review and the study will not be initiated until Nationwide Children's Hospital's IRB approval has been obtained. Any amendments to the protocol or consent materials will also be approved before they are placed into use.

11.3 Informed Consent Process

Informed consent is a process that is initiated prior to the individual's agreeing to participate in the study and continuing throughout the individual's study participation. Extensive discussion of risks and possible benefits of this therapy will be provided to the parents or guardians of the subjects. Consent forms describing in detail the study interventions/products, study procedures, and risks are given to the parent or guardian of the subject and written documentation of informed consent is required prior to starting intervention/administering study product. Consent forms will be IRB-approved and the parent or guardian of the subject will be asked to read and review the document. Upon reviewing the document, the investigator will explain the research study to the parent or guardian of the subject and answer any questions that may arise. The subject's parent or guardian will sign the informed consent document prior to any procedures being done specifically for the study. The parent or guardian of the subjects should have the opportunity to discuss the study with their surrogates or think about it prior to agreeing to participate. The parent or guardian of the subjects may withdraw consent at any time throughout the course of the trial. A copy of the informed consent document will be given to the parent or guardian of the subjects for their records. The rights and welfare of the subjects will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

11.3.1 Informed Consent/Assent Process (in Case of a Minor)

Assent is not applicable to this patient population.

11.4 Subject Confidentiality

Subject confidentiality is strictly held in trust by the participating investigators, their staff, and the sponsor(s) and their agents. This confidentiality is extended to cover testing of biological samples and genetic tests in addition to the clinical information relating to participating subjects.

The study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the sponsor.

11.5 Study Discontinuation

In the event that the study is discontinued, the subjects will receive ketorolac at the discretion of their treating physician.

12 DATA HANDLING AND RECORD KEEPING

12.1 Data Management Responsibilities

All source documents and laboratory reports must be reviewed by the clinical team and data entry staff, who will ensure that they are accurate and complete. Adverse events must be graded, assessed for severity and causality, and reviewed by the PI or designee.

Data collection is the responsibility of the clinical trial staff under the supervision of the PI. During the study, the investigator must maintain complete and accurate documentation for the study.

12.2 Data Capture Methods

Clinical data, including AEs, concomitant medications, and clinical laboratory data will be entered into a password protected data. Clinical data will be entered directly from the source documents.

12.3 Types of Data

Data for this study will include safety, laboratory, and outcome measure.

12.4 Study Records Retention

Study documents should be retained per Nationwide Children's Hospital policy.

12.5 Protocol Deviations

Each patient will be reviewed actively while on the study by the study staff. A protocol deviation is any noncompliance with the clinical trial protocol, Good Clinical Practice (GCP), or Manual of Procedures requirements. The noncompliance may be either on the part of the subject, the investigator, or the study site staff. As a result of deviations, corrective actions are to be developed by the site and implemented promptly. The safety of the patient/subject will not be compromised by the study protocol.

13 PUBLICATION POLICY

Following completion of the study, the investigator is expected to publish the results of this research in a scientific journal. The International Committee of Medical Journal Editors (ICMJE) member journals have adopted a trials-registration policy as a condition for publication. This policy requires that all clinical trials be registered in a public trials registry such as ClinicalTrials.gov*, which is sponsored by the National Library of Medicine. Other biomedical journals are considering adopting similar policies.

*Journal Citation:

De Angelis C, Drazen JM, Frizelle FA, Haug C, Hoey J, Horton R, et al. Clinical trial registration: a statement from the International Committee of Medical Journal Editors. N Engl J Med. 2004;351:1250-1.

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15 SUPPLEMENT/APPENDICES

15.1 Table 1: Pharmacological management of post-operative pain associated with common neonatal surgical procedures.

Degree of Pain	Surgeries included	Post-Op Pain Management
Potential for **Severe Pain**	Closure gastroschisis/ omphalocele under tension Complicated NEC CDH repair Exploratory laparotomy TEF/EA repair Nissen fundoplication / Gastrostomy tube Bowel re-anastamosis Wound debridement Cloacal exstrophy repair Thoracotomy Open abdomen/compartment syndrome Open liver biopsy / cholangiogram PDA ligation Tracheostomy	1. Escalation: increased opiate dosing a minimum of 50% & increase PRN opiate dose / evaluate for addition of ketolorac, **2. continuous infusion opiate + PRN opiate for breakthrough pain** **Morphine 0.05 mg/kg/hr + morphine 0.05 mg/kg q1hrs prn** **OR** **Fentanyl 2 mcg/kg/hr + fentanyl 2 mcg/kg q1hr prn** **Plus** 3. De-escalation**:** decrease infusion 50% or change to scheduled intermittent opiate + PRN opiate for breakthrough pain
Potential for **Moderate Pain**	Closure of gastroschisis/omphalocele-no tension Repair incarcerated/giant hernia Abdominal drain or chest tube insertion Myelomeningocele repair Colostomy Primary laparoscopic pull through Large cystic hygroma resection	1. Escalation**:** change to continuous infusion opiate **2. scheduled intermittent opiate + PRN opiate for breakthrough pain** **Morphine 0.05 mg/kg/dose q3hrs + morphine 0.05 mg/kg/dose q1prn** 3. De-escalation**:** scheduled APAP ± PRN opiate
Potential for **Mild Pain**	Uncomplicated inguinal hernia Perineal approach for Hirschsprung's disease Perineal repair of imperforate anus/ anoplasty VP / subgaleal shunt placement Retinal laser surgery Gastrostomy tube insertion	1. scheduled opiate + PRN APAP **2. scheduled APAP* + prn opiate for breakthrough pain** **scheduled APAP* + morphine 0.05 mg/kg/dose q1hrs prn** 3. non-pharmacologic

***APAP = acetaminophen dosing based on age (see table 2)**

15.2 Table 2

Non-opiod analgesics	
Acetaminophen supp	LD: 25-40 mg/kg MD: <28 wks: no data 28-32 wks: 20mg/kg q12° (max 40mg/kg/day) 32-36 wks or ≥37 wks and <10 days old: 15mg/kg q8° (max 60mg/kg/day) ≥37 wks and >10 days old: 20mg/kg q6-8° (max 90mg/kg/day) Note: Use caution in patients with liver abnormalities and/or hyperbilirubinemia. A maximum of 24 hours of APAP can be used in this population unless a specialist is consulted.
Ketorolac	≥37 weeks and ≥ 1 weeks of age 0.5mg/kg q8° ≥ 44 weeks may increase to 0.5 mg/kg/dose q6hrs if needed maximum of 5 days of therapy ***do not use the first week of life ***do not use is estimated CrCl <30 ml/min** Note: DO NOT USE in patients with history of GI perforation, ulcer, thrombocytopenia, liver dysfunction,and/or bleeding due to increased risk of GI bleeding[8]

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