Protocol title: Single center, randomized double blind, placebo controlled trial to evaluate the safety and efficacy of acetaminophen in preterm infants used in combination with ibuprofen for closure of the ductus arteriosus.

Drug substance Investigated: Oral acetaminophen

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Background

Ductus arteriosus is a vital arterial connection between the pulmonary and systemic fetal circulation. It allows blood enriched in oxygen and nutrient, returning from the placenta, to bypass the lungs and to readily reach the lower parts of the body of the fetus. This flow of blood from the pulmonary circulation to systemic circulation is driven by the higher pulmonary vascular resistance and pressure as compared to the systemic ones. After birth, as pulmonary circulation dilates and pulmonary vascular pressure and resistance decrease, all right ventricular cardiac output shifts to the lung and subsequently the ductus arteriosus closes.

In preterm infants, the ductus arteriosus may remain open after birth, known as persistent PDA (pPDA). Approximately 50% of preterm infants with birth weight <1000 g develop pPDA. As the incidence of a pPDA is inversely proportional to birth weight (BW) and gestational age, a hemodynamically active *PDA (defined as carrying a significant blood flow from the aorta to the lung)* is a very common morbidity in extremely low birth weight infants (ELBWI, BW <1000 grams). After birth, the blood flowing through a PDA contributes to a higher pulmonary blood flow, *(significant left to right shunt, Aorto-pulmonary shunt)* leading to left ventricular overload. As a result, hemodynamically significant pPDAs are associated with prolonged mechanical ventilation, and higher occurrences of hypotension, pulmonary hemorrhage, bronchopulmonary dysplasia, necrotizing enterocolitis, retinopathy, intraventricular hemorrhage, and abnormal cerebral and intestinal perfusion in the ELBWI[1, 2, 3, 4].

The mechanism of pPDA in ELBWI is not well known. Failure of the ductus arteriosus to constrict may be partly mediated by the immaturity of the signaling pathways for vasodilators and vasoconstrictors. After birth, all newborn infants are exposed to a sudden oxidative stress and experience a surge in the reactive oxygen species (ROS). These ROS contribute to the closure of the PDA after birth. Prostaglandin F2 a (PGF2a) is an established marker for oxidative stress and also produces smooth muscle cell contraction (used to induce labor). Elevated levels of PGF2a are usually found in all newborn infants during the first weeks of age. Chen, et al., have found that PGF2a produces ductal closure in mature mice born at term gestational age while it induces dilation of the

ductus in preterm mice[5]. In addition, the ductus arteriosus in preterm infants has an increased sensitivity to vasodilators, such as prostaglandin E2 and to nitric oxide [6,7].

NSAIDs (non-steroidal anti-inflammatory drugs) inhibit the production of prostaglandins by their non-selective inhibition of the cyclooxygenase-1 and cyclooxygenase-2 (COX-1 and COX-2)[8]. They are the first line of therapy for hemodynamically active PDAs (significant aorta-pulmonary shunt). However, the undesirable complications associated with NSAIDs, such as necrotizing enterocolitis and isolated small bowel perforation, limit their daily dosage and their duration of therapy. In addition, their ability to close a patent ductus arteriosus decreases with lower gestational age. Higher mortality and morbidity rates are associated with failure to close a PDA[9, 10]. Failure to respond to treatment will require successive courses of ibuprofen or may resort to surgical intervention. Published reports have demonstrated high rates of long term neurological complications associated with surgical closure of a ductus arteriosus [11,12].

Recently, two randomized controlled studies found that the effectiveness of oral acetaminophen was equivalent to the use of oral ibuprofen as a first line treatment of PDAs in preterm infants[13 14]. Recently performed RCT, comparing intravenous administration of ibuprofen, indomethacin and acetaminophen, has found that intravenous administration of acetaminophen has similar efficacy in constricting the ductus when compared to the standard treatment regimens involving indomethacin and ibuprofen. This study also found very high rate of ductal constriction, 80%, in preterm infants who received IV acetaminophen, higher than the previously reported rates.[17] In addition, acetaminophen appears to have selective inhibitory actions on COX-2 [15]. Furthermore, COX-2 inhibitors were able to constrict the ductus arteriosus in fetal lambs [16].

While acetaminophen seems a promising alternative to Ibuprofen, it could add its beneficial constrictive effects on the ductus arteriosus without potentiating similar undesirable effects seen with NSAIDs. Inability to close the ductus arteriosus with ibuprofen is common (more than 30%), leading to prolonged duration of ventilation, unstable cardiovascular system, and higher occurrence of long term morbidities. The combination of acetaminophen and ibuprofen therapy could be beneficial and may improve the ductal constriction rate when compared to the regimen wherein they are used alone. This combined therapy is under investigation currently. Out Of two studies conducted, one study has been published recently.[18] Other study is still recruiting the infants. The published study demonstrated a trend towards higher rates of PDA closure among infants treated with combination of ibuprofen and acetaminophen as opposed to ibuprofen alone. No increased risk for adverse events reported in that study.

Hypothesis

The hypothesis is to determine whether treatment of hemodynamically significant PDA with a combined therapy of intravenous Ibuprofen and oral acetaminophen has higher success rate in closing the ductus arteriosus than standard ibuprofen alone therapy in preterm infants.

1) **Primary outcome:**

Ductal closure/constriction rate as defined based on the echocardiographic findings. Ductal closure/constriction will be defined as the complete closure of ductus or ductal diameter <1 mm.

2) **Secondary outcome:**

Echocardiographic ductal parameters before and after intervention: ductal size, Left atrium to aortic root ratio, ductal velocity, descending aortic diastolic flow

Ventilator parameters and oxygenation index before and after intervention
Ventilation days
Duration of Oxygen treatment
Duration of CPAP
Total no. PDA treatments after the study interventions
Need for PDA ligation
BPD at 36 weeks
Home Oxygen need
Retinopathy of prematurity
Feeding intolerances
Gastrointestinal perforation
Necrotizing enterocolitis
Gastrointestinal hemorrhage
Duration of hospital stay
Duration of TPN
Late onset sepsis
Need for late corticosteroid treatment post study intervention

3) Safety outcomes

Death
Elevated liver enzymes
Acute kidney injury
Feeding intolerance while on study intervention
GI hemorrhage
Intestinal perforation after the initiation of study intervention
NEC after the initiation of study intervention
Thrombocytopenia

Data collection;
All the pertinent baseline maternal and neonatal clinical-sociodemopgraphic data will be collected prospectively by accessing the maternal and neonatal electronic medical records. All the pertinent postnatal clinical, biochemical and echocardiographic data will be collected prospectively all the newborn infants enrolled in the study so as to define all the primary, secondary and safety outcome variables. Even if infant is withdrawn from the study, data collection will be continued as it is an intention-to-treat analysis.

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Methods

Study type: This study is a single center, randomized, double blinded, placebo controlled trial

Population: Preterm infants with gestational age of with a gestational age ≤27 $^{6/7}$ weeks by the best obstetric estimate.

Sample size estimation: A chart review was conducted to assess the success rate of PDA closure after the first course of ibuprofen among ELBWI. It was determined that 60% of ELBWI treated for a persistent PDA with ibuprofen did not need a second course or surgical intervention. Aa total sample size of 72 ELBWI would be required to detect at least a 30% absolute increase (from 60% to 90%) in the success rate of PDA closure using combined ibuprofen-acetaminophen therapy with a type II error of .20 (power of 80%) and a type I error of .05 (two-tailed). Due to a possibility of withdrawal of infants from the study, due to feeding intolerance, poor tolerance to oral acetaminophen or made NPO for other reasons, sample size will inflated by 10% Hence, total no. infants required will be 80. Analysis will be based on intention-to treat.

Inclusion criteria:

Infants will be included in the study if ALL three following criteria are met:

1. Written parental consent is obtained
2. Infant requires respiratory support (assisted ventilation or CPAP)
3. diagnosis of a persistent hemodynamically significant PDA after 5 days of age, defined as ductal size ≥ 1.5 mm and at least one of the followings:

    a) Maximum flow velocity through the ductus ≤ 2 m/s
    b) Left atrium to aorta ratio ≥ 1.4
    c) Wide pulse pressure
    d) Elevated BNP > 200
    e) systemic hypoperfusion: metabolic acidosis with base deficit ≥ 10 mEq/L
4. Attending neonatologist made decision to treat PDA

Exclusion criteria:

1. No parental consent
2. Infants < 5 days and > 21days of postnatal age
3. Congenital anomalies such as cardiac or multiple anomalies
4. Infection (e.g., septicemia, pneumonia)
5. Bleeding disorder or platelet count< 50,000/ml
6. Acute kidney injury (AKI)defined as oliguria (urine output< 0.5 ml/kg/hr for 16hrs) and/or serum creatinine > 1.5 mg/dl
7. Elevated liver enzymes (>2 fold normal levels)
8. Pulmonary hypertension or right to left shunt through the ductus arteriosus
9. Diagnosis of necrotizing enterocolitis
10. Unable to tolerate oral medications or NPO at the time of enrollment. (if NPO after enrollment, withdrawn from the study)
11. Infants on postnatal corticosteroid treatment for treating parenchymal lung disease

Study Objectives and overview:

The primary objectives of the study are to confirm the safety of oral acetaminophen in extremely low

birth infants, given concomitantly with ibuprofen and also to determine its efficacy in significantly increasing the rates of ductal closure when compared to only ibuprofen therapy. Hence primary outcome variable include PDA closure success rate, based on the 2-D transthoracic echocardiographic evidence, with in the time frame of seven days following the study interventions. Secondary objectives are to exclude the need for further medical management to close PDA which includes subsequent intravenous ibuprofen courses (standard of care) or surgical intervention to close the ductus arteriosus (surgical PDA ligation), duration of mechanical ventilation, requirement of steroid therapy, incidence of necrotizing enterocolitis, small bowel perforation, bronchopulmonary dysplasia, nosocomial sepsis, retinopathy of prematurity, and death.

Randomization:

The study population will be stratified to two subgroups based on gestational age *(GA ≤24 weeks and ≥ 25 weeks)*. Randomization will occur by using computer generated random sequence, using a 4-block design, with 1:1parallel allocation. Allocation group (either treatment group or placebo group) will be labelled on a card and the card will be sealed in an opaque envelope. The sealed envelope will be labelled serially and opened sequentially after enrolling infants in to the study. The pharmacist will pick the envelope corresponding to the subgroup of the patient, based on subject's gestational age.

Several small, sealed, non-transparent, and serially numbered envelopes will be placed into one large envelope. The pharmacist will open a small envelope with the lowest serial number (next available number). In each of these small envelopes is an assigned treatment with a second card detailing the labs required for the study. The pharmacist will distribute the second a card to the lab personnel, detailing the labs needed on the blood sample collected.

Protocol

An infant is randomized into the study if all inclusion criteria are met.

Before the beginning of the intervention:

A.

1. Confirm the presence of parental consent in the chart
2. Check if infant is on caffeine citrate. If he/she is not, start the infant on caffeine citrate per standard caffeine orders and standard unit's policy.
3. CBC with diff (if baseline CBC not available), BUN, creatinine, BNP (if baseline BNP not available), AST and ALT
4. Collect urine for specific gravity
5. Confirm that infant has appropriate urine output (> 4 wet diapers per day)

B. Randomization:

1. Order written to treat PDA per study protocol

2. Infant will be randomized by a pharmacist to one of the two treatment arms.

    a) Ibuprofen-acetaminophen arm (intervention arm): lbuprofen and acetaminophen will be administered concomitantly.

    Intravenous Ibuprofen is the mode of administration. The dose of ibuprofen will be the standard dose used in our NICU, which include dosing based on the postnatal age. Infants < 70 h of age: 10 mg/kg/dose loading dose followed by 5 mg/kg/daose, two doses at q24

intervals, started 24 h after the loading dose. Infants aged 70 -108 h: 14 mg/kg/dose loading dose followed by 7 mg/kg/dose, two doses at q24 intervals, started 24 h after the loading dose. Infants > 108 h: 18 mg/kg/dose loading dose followed by 9 mg/kg/dose, two doses at q24 intervals, started 24 h after the loading dose. This ibuprofen dosing regimen is as per the standard of care at our NICU. Acetaminophen will be administered as oral formulation d. Acetaminophen is given at a dose of 15 mg/Kg q 6 hours for 3 days (complete total of 12 doses). Intervention will be only for 3 days. After three days of intervention, if PDA still open, decision to close and medication choice will be as per the attendings' discretion and as per our standard of care.

b) Ibuprofen-placebo arm (control arm): Intravenous Ibuprofen is the mode of administration. The dose of ibuprofen will be the standard dose used in our NICU, which include dosing based on the postnatal age. Infants < 70 h of age: 10 mg/kg/dose loading dose followed by 5 mg/kg/dose, two doses at q24 intervals, started 24 h after the loading dose. Infants aged 70 -108 h: 14 mg/kg/dose loading dose followed by 7 mg/kg/daose, two doses at q24 intervals, started 24 h after the loading dose. Infants > 108 h: 18 mg/kg/dose loading dose followed by 9 mg/kg/dose, two doses at q24 intervals, started 24 h after the loading dose. This ibuprofen dosing regimen is as per the standard of care at our NICU Placebo will be sterile water, with similar volume and color as acetaminophen, will be given through the oro-gastric tube, for three days at 6 h intervals. Intervention will be only for 3 days. After three days of intervention, if PDA still open, decision to close and medication choice will be as per the attendings' discretion and as per our standard of care.

Day1-3 of intervention:

1. Urine output and urine specific gravity monitored daily
2. Blood specimen collected and sent to lab for acetaminophen serum levels before the 8th dose.
3. Obtain s. creatinine if oliguria (urine output< 0.5 ml/kg/hr for 16 hrs) develops

Day 4 (+ 2 days) of intervention (after the completion of 3 days of treatment)

1. Obtain echocardiogram to assess the presence of a PDA. Preferably on day 4. If facility is not available, obtain within next 2 days.
2. CBC with diff count, BNP and BUN, serum creatinine, ALT and AST and BNP
3. The study interventions end after the 3 days of treatment. If PDA remains patent, it will be at the discretion of the attending to consider treatment or not. Medication use will be at the discretion of the attending. PDA will be managed as per our standard of practice. However, all the pertinent data will be collected prospectively for the analysis.

Withdrawal of subject from the study

The study intervention will be stopped immediately and subject will be withdrawn from the study if any of the following occur:

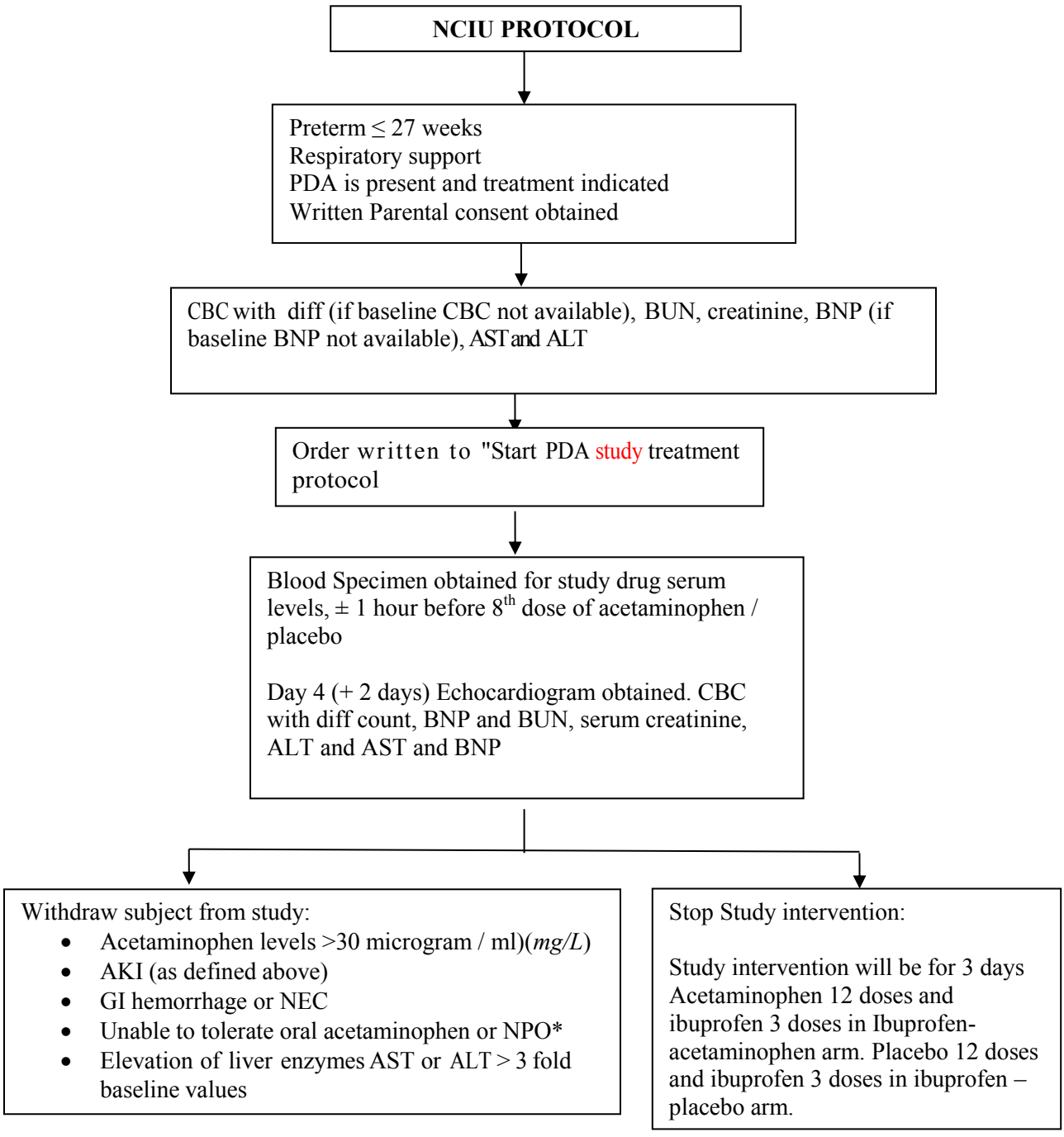
1. Acetaminophen trough levels >30 microgram/ml (mg/L). This critical value will be called to the clinical team.
2. Elevation of liver enzymes AST or ALT > 3 fold baseline values
3. Stage 2 or greater neonatal AKI is determined by oliguria (urine output< 0.5 ml/kg/hr for 12 hrs) and/or S.cr increases by 200% from baseline(≥ 2 fold increase). This definition is as per Kidney

Diseases Improving global Outcomes (KDIGO) neonatal AKI definition.

4. Gastrointestinal bleeding
5. Necrotizing enterocolitis
6. Unable to tolerate oral acetaminophen or made NPO for feeding intolerance

Ordering laboratory tests for monitoring

Blood samples will be obtained from all enrolled infants baseline, before the eighth dose of acetaminophen or placebo and after the completion of the study intervention . The blood sample will be labelled as "Study labs". Lab supervisors will have access to the randomization list and will identify infants randomized to acetaminophen and Ibuprofen arm to run the acetaminophen lab levels. All the infants enrolled in the study will be tested for BNP, LFTs and serum creatinine as standard of care.



*NPO during study: If infant is placed NPO while on study drug, enteral meds (acetaminophen or placebo) will be held. Infant will be withdrawn from the study.

PDA Treatment Protocol to Pharmacy

Pharmacist will open the next available envelope that assign the infant to one of the two groups Infants randomized to the Ibuprofen-acetaminophen arm will receive

- Ibuprofen dosing as per the standard of care at our NICU: The dose of ibuprofen will be the standard dose used in our NICU, which include dosing based on the postnatal age. Infants < 70 h of age: 10 mg/kg/dose loading dose followed by 5 mg/kg/dose, two doses at q24 intervals, started 24 h after the loading dose. Infants aged 70 -108 h: 14 mg/kg/dose loading dose followed by 7 mg/kg/dose, two doses at q24 intervals, started 24 h after the loading dose. Infants > 108 h: 18 mg/kg/dose loading dose followed by 9 mg/kg/dose, two doses at q24 intervals, started 24 h after the loading dose. This ibuprofen dosing regimen is as per the standard of care at our NICU
- PO Acetaminophen at 15 mg/kg q 6 hours x12 doses
- Discontinue acetaminophen after dose #12.
- If infant is NPO; the subject will be withdrawn from the study.

Infants randomized to the Ibuprofen-placebo arm will receive

- Ibuprofen dosing as per the standard of care at our NICU: The dose of ibuprofen will be the standard dose used in our NICU, which include dosing based on the postnatal age. Infants < 70 h of age: 10 mg/kg/dose loading dose followed by 5 mg/k/dose, two doses at q24 intervals, started 24 h after the loading dose. Infants aged 70 -108 h: 14 mg/kg/dose loading dose followed by 7 mg/kg/dose, two doses at q24 intervals, started 24 h after the loading dose. Infants > 108 h: 18 mg/kg/dose loading dose followed by 9 mg/kg/dose, two doses at q24 intervals, started 24 h after the loading dose. This ibuprofen dosing regimen is as per the standard of care at our NICU
- Placebo (sterile water) q 6 hours x 12 doses
- Discontinue placebo after dose #12 if PDA closed.
- If infant is NPO; the subject will be withdrawn from the study.

Pharmacy

The pharmacist will randomly assign the subject to one treatment arm. Randomization to treatment arm will be performed by using randomly assigned, serially numbered envelopes. The population will be stratified to two subgroups based on gestational age GA ≤24 weeks or GA ≥ 25 weeks. The randomization will be performed after the subject has been assigned to one of the 2 subgroups.

Medication storage

The medication will be stored in a segregated area of the pharmacy designated for study medications.

Intravenous Ibuprofen preparation:

Intravenous ibuprofen is available in a standard concentration of 10 mg/ml. This available standard concentration will not be further diluted. Intravenous ibuprofen will be dosed as described above. Patient specific doses will be drawn up by pharmacist and dispensed.

Oral acetaminophen preparation

Acetaminophen will be dispensed as a 160 mg/5 ml (32 mg/ml) solution. Each dose will be calculated

and rounded to the nearest 0.01mi. Patient specific doses will be drawn up, labeled as study drug, and dispensed in an opaque syringe.

Oral Placebo preparation

Placebo will be sterile water without any added flavor or dextrose. Acetaminophen will be dye free, no added coloring agents will be used. The volume dispensed will be the same as the volume that would be dispensed if the subject is assigned to study drug. Each dose will be labeled as study drug and dispensed in an opaque syringe.

Table of medication volumes

Acetaminophen (32 mg/ml)		**Placebo**
15 mg/kg	Vol Dispensed	Vol Dispensed
4.5mg	0.14ml	0.14 ml
5.25 mg	0.16ml	0.16ml
6mg	0.19 ml	0.19 ml
6.75 mg	0.21ml	0.21ml
7.5 mg	0.23ml	0.23 ml
8.25 mg	0.26ml	0.26 ml
9mg	0.28ml	0.28 ml
9.75 mg	0.3ml	0.3 ml
10.5 mg	0.33ml	0.33 ml
11.25 mg	0.35ml	0.35ml
12 mg	0.38ml	0.38ml
12.75 mg	0.4ml	0.4ml
13.5 mg	0.42 ml	0.42ml
14.25 mg	0.45 ml	0.45ml
15 mg	0.47ml	0.47 ml

Study drugs will be monitored by the pharmacist and recorded on the medication dispensing record.

Rationale for acetaminophen dosage, schedule, and serum levels

Acetaminophen is a commonly used drug in all ages. In newborns, it is commonly given for prevention or treatment of fever related to vaccinations. Although its use is safe in newborn infants, its pharmacokinetic characteristics are not well known.

The table below (Table 1) shows a summary of published reports about preterm patients who received oral acetaminophen for ductal closure. After examining these reports, a conclusion can be made that oral administration of acetaminophen may be safe at a dose of 15 mg/kg every 6 hours for three to six days. None of these studies found any undesirable effect from the use of acetaminophen. Liver enzymes remain normal in all studies, except for the Dang, et al, study which did not report these values. In addition, acetaminophen seems to be useful in closing the PDA of preterm infants. Oral acetaminophen was associated with a 66% closure of the hemodynamically active PDAs (100 out of 152 infants experienced a closure of their PDA).

Although acetaminophen, used for ductal closure, was not associated with any major complications, its pharmacokinetics in extremely low birth weight infants remain uncertain. This uncertainty warrants the monitoring of acetaminophen serum levels.

Holding or stopping feeds for 1-2 days is a common occurrence in preterm infants. Infants who are not able to tolerate enteral milk or meds at the beginning of the study will not be included in the study. However, for infants who have been feeding and were included in the study, if the clinical care team decides to hold their enteral feeds and meds, infant will be withdrawn from the study intervention. Management will be as per the standard practice in the NICU and will be at the discretion of attending neonatologists. .

Table 1. Published Reports using Oral Acetaminophen for PDA Closure

Authors/GA	**Mode/dose of Acetaminophen**	**N**	**Duration (days)**	**Closed**	**Elevated LFT**
EI-Khuffash[1] 2014 GA 26 weeks	Oral 15/kg q6hr Oral 15/kg q6hr IV 15/kg q6hr	N=5 N=7 N=9	2 7 2-6	0/5 1/7 5/9	0
Dang et al [2] 2013 GA 31weeks	Oral 15/kg q6hr	N=80	3	45/80	Not mentioned
OnceI et al[3] 2014 GA 27 weeks	Oral 15/kg q6hr	N=40	3	29/40	0
Hammerman 2011 GA 26-32 weeks	Oral 15/kg q6hr	N=5	2-3 (some 7)	5/5	0
Jasaniet al [4] 2013 GA 26-32 weeks	Oral15/kg q6hr	N=6	3 (some 6)	6/6	0

Ozdemiret al[5] 2014 GA 23-32 weeks	Oral 15/kg q6hr	N=7	3 (some 7}	5/7	0
Kesselet al[6] 2014 GA 26-30 weeks	Oral15/kg q6hr	N=7	3 (some 7)	5/7	0
Nadir et al[7] 2014 GA 24-27 weeks	Oral15/kg q6hr	N=7	Up to 7	5/7	0

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DATA AND SAFETY MONITORING PLAN (DSMP)

Study title: Safety and efficacy of acetaminophen in extremely low birth infants used in addition to ibuprofen for ductal closure.

Risk Classification of the study: Greater than minimal risk, but presenting the prospect of direct benefit to the individual subject.

Type of Research data/events to be monitored:

The efficacy of acetaminophen will be monitored by echocardiogram, assessing the size of the lumen of the ductus arteriosus. Echocardiograms are standard procedures which are routinely used for the diagnoses and monitoring of PDA therapy in preterm infants. Drug safety factors will be assessed daily during the treatment.

All blood and urine sample tests included in this study are routinely performed in preterm infants who are diagnosed or treated for a persistent patent ductus arteriosus, except for acetaminophen serum levels.

In addition to serum liver enzymes and creatinine, two acetaminophen serum levels will be obtained during the study treatment; each consists of 0.2 ml of blood.

Most of premature infants have umbilical arterial catheter in the first 2 weeks of life. Blood samples will be obtained directly from these catheters. In infants who do not have an indwelling catheter, blood sample will be obtained by a heel stick.

Persons Responsible for Data Monitoring

Gina Massey, RN and Ellen Dean, RN will monitor for any adverse event or unanticipated problems. In addition, independent data safety monitoring board (DSMB) will perform safety monitoring by running interim analyses. DSMB will be provided with deidentified blinded data. Dr. Ariel Salas, Assistant Professor of Pediatrics, neonatology division, University of Alabama at Birmingham will serve as DSMB chair. He will be assisted by two other attending neonatologists. DSMB will perform 3 interim analyses as indicated below. He will also give recommendations to continue or stop the trial based on the pre-specified criteria elaborated below.

Reporting unanticipated problem, adverse events, protocol deviation or violation:

Any unanticipated problem or adverse event that occurs during the study treatment or anytime during the follow-up period (one week after the completion of therapy) will be assessed by pharmacists, nurses, physicians caring for the infant, monitoring team, and hospital administrators. Mortality and life threatening morbidities will be evaluated as soon as possible (within 24 hours) by the monitoring team. The monitoring team will notify parents immediately and notify the IRB within 5 business days.

It is the responsibility of the monitoring team to decide if an event is a protocol deviation (*does not affect safety or efficacy*) or violation (*deviation from the approved IRB protocol or may potentially affect the infant*). Any protocol violation or deviation will be will be reported within 5 business days to the IRB.

Procedures and Time frames for communicating outcomes:

Patient medical information (vital signs, respiratory support, fluid intake, output, medications, and blood test results) will be collected, entered in encrypted Excel files, and stored on password protected computers. Computers are kept in secure (C-WEB) area of the hospital.

While adverse events will be investigated without any delay, all other patient data will be analyzed at 25%, 50% and 75% completion of study population enrollment. Report to IRB will be sent after every DSMB meetings. The project is expected to last for about 4 years.

Emergency actions: Unblinding-

Pharmacists and laboratory staff are not blinded to the study. A root cause analysis will be performed after any adverse event. The monitoring team and pharmacists will evaluate if the event is related to the study treatment. If this is the case, the treatment will be shared with the clinical team and parents.

Withdrawal subject from the study-

The study intervention will be stopped if any of the following occur:

a. Elevation of liver enzymes AST or ALT > 3 fold baseline values. These results will be available for the team caring for the baby
b. Acetaminophen trough serum levels> 30 microgram/ml (mg/L) will be called to the nursery as critical value.
c. AKI stage 2 or greater (as defined above)
d. gastrointestinal bleeding
e. Necrotizing enterocolitis
f. NPO

Rules for stopping the study:

DSMB will meet and analyze the data after the enrollment of 25%. 50% and 75% of study population and will decide about to continuation/discontinuation of the study.

The study will be stopped as per DSMB recommendations if following pre-specified criteria are met

1) Haybittle-Peto boundary will be used for stopping the study based on the efficiency of treatment arm

No. interim analyses	Interim analyses	P value boundary
3	1	0.001
	2	0.001
	3 (final)	0.05

2) Pocock boundary will be used for adverse event or futility monitoring (p value 0.0221), which is same at each interim analysis. Interim analyses will be performed more often, every month, for

futility testing.

Precautions for maintaining data integrity:

The goal of the principal investigator, other investigators and team monitors is to find the best and safest treatment for sick preterm infants. No financial or other non-monetary gain will be obtained by any of the investigators or monitors.

All collected data will remain confidential even after the study is completed. It is also kept secured as detailed above. However, although data will be safe from unauthorized access, it will still be accessible to authorized users (monitor team and principal investigator). In addition, data will be backed up weekly in addition to keeping a copy with each of the monitoring team members.

Secondary data analysis:

Persistent PDA among extremely low birth weight infants is common. Incidence of persistent PDA is inversely related to gestational age and severity of respiratory distress syndrome. Late postnatal corticosteroids use has shown to decrease the composite outcome of death or BPD among high risk preterm infants by attenuating the pulmonary inflammation and improving the lung compliance. Hence, late postnatal corticosteroid might influence the hemodynamics of PDA among extremely preterm infants and enable extubation by improving lung compliance despite of persistent PDA. However prospective data on the influence of corticosteroid on the natural course of PDA among ELBWI is lacking. Data collected for this RCT will be used to analyze natural course of PDA among preterm infants who are treated with late postnatal corticosteroids.

As PI of this research study, I endorse the information in this DSMP for I acknowledge that,as a PI,I am responsible for implementation of the DSMP by all members of the research team.

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Investigator Signature Date