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# Acetaminophen versus ibuprofen in the management of hemodynamically significant patent ductus arteriosus in very low birth weight infants

**Submission date**
31/08/2023

**Recruitment status**
No longer recruiting

**Registration date**
17/09/2023

**Overall study status**
Completed

**Last Edited**
11/09/2023

**Condition category**
Neonatal Diseases

[ ] Prospectively registered
[ ] Protocol
[ ] Statistical analysis plan
[ ] Results
[ ] Individual participant data
[ ] Record updated in last year

## Plain English summary of protocol

Background and study aims
A hemodynamically significant Patent Ductus Arteriosus (hs-PDA) is a condition where a small blood vessel that should close after birth remains open. To date there is no definitive study regarding what would be the best pharmacological (drug) treatment for closure of a hs-PDA. The aim of this study is to evaluate the effectiveness and safety of acetaminophen versus ibuprofen in the treatment of hs-PDA.

Who can participate?
Preterm newborns between 25+0 – 31+6 weeks of gestational age and/or ≤1500 g birth weight; with a diagnosis of hs-PDA within the first 2 weeks after birth; admitted to the neonatal intensive care unit of Guillermo Grant Benavente Hospital.

What does the study involve?
Preterm infants are randomly allocated into acetaminophen or ibuprofen treatment groups. The evaluation of hs-PDA closure is performed 1 day after treatment. A blood count and renal and liver function tests will be carried out after treatment.

What are the possible benefits and risks of participating?
The participants will contribute to defining the best pharmacological alternative for the treatment of patent ductus arteriosus. The drugs studied are commonly used for this purpose, so participation in this study does not entail an added risk to the expected effects for the usual treatment of patent ductus arteriosus (renal failure, liver dysfunction, gastrointestinal bleeding).

Where is the study run from?
Guillermo Grant Benavente Hospital (Chile)

When is the study starting and how long is it expected to run for?
January 2017 to December 2019

Who is funding the study?
Investigator initiated and funded

Who is the main contact?
Dr Andrés Marinovic, marinovic.ped@gmail.com

# Contact information

### Type(s)
Public

### Contact name
Dr Andres Marinovic

### Contact details
Alto Horno 777, Talcahuano - Las Higueras Hospital, Neonatology Service
Talcahuano
Chile
4260000
+56 (0)41 268 7000
marinovic.ped@gmail.com

### Type(s)
Scientific

### Contact name
Dr Andrés Marinovic

### Contact details
Alto Horno 777, Talcahuano - Las Higueras Hospital, Neonatology Service
Talcahuano
Chile
4260000
+56 (0)41 268 7000
marinovic.ped@gmail.com

### Type(s)
Principal Investigator

### Contact name
Dr Aldo Bancalari

### Contact details
Paicaví 255 Of.1, Concepción
Concepción
Chile
4030000
+56 (0)41 223 7371
aldobancalari@gmail.com

# Additional identifiers

**EudraCT/CTIS number**
Nil known

**IRAS number**

**ClinicalTrials.gov number**
Nil known

**Secondary identifying numbers**
Nil known

# Study information

**Scientific Title**
Acetaminophen versus ibuprofen in the management of hemodynamically significant patent ductus arteriosus in very low birth weight infants: a randomized controlled trial

**Acronym**
PDA-AVSI

**Study objectives**
Acetaminophen has an effectiveness similar to ibuprofen in closing hemodynamically significant patent ductus arteriosus with fewer side effects.

**Ethics approval required**
Ethics approval required

**Ethics approval(s)**
Approved 15/05/2017, Scientific Ethical Committee of the Concepcion Health Service (O´Higgins 297, Concepción, 4030000, Chile; +56 (0)41 2721795; cec@ssconcepcion.cl), ref: 17-04-20

**Study design**
Single-center interventional single-blinded randomized controlled trial

**Primary study design**
Interventional

**Secondary study design**
Randomised controlled trial

**Study setting(s)**
Hospital

**Study type(s)**
Treatment, Safety, Efficacy

**Participant information sheet**

Not available in web format, please use the contact details to request a participant information sheet

## Health condition(s) or problem(s) studied
Patent ductus arteriosus in the very low birth weight premature newborn

## Interventions
This was a randomized prospective study in very low birth weight preterm newborns <32 weeks GA and/or ≤1500 g with an echocardiographic diagnosis of hs-PDA, performed during the first 2 weeks of life, between January 2017 to December 2019.

The diagnosis of hs-PDA was made by echocardiography using two-dimensional color Doppler (Vivid-i, GE Healthcare), carried out by a pediatric cardiologist who was blinded to the study treatment groups.

The echocardiographic criteria to define hs-PDA were: ductal diameter ≥1.5 mm or equal to or greater than that of the left pulmonary artery (LPA), measured in the right parasternal short axis; left cavities dilation or left atrial-aortic ratio (Ai/Ao) >1.4, measured in the left parasternal long axis; retrograde flow measured in the descending aorta, celiac or mesenteric artery.

Patients who met the inclusion criteria were randomized to acetaminophen or ibuprofen group, using an opaque sealed envelope, sequentially numbered. The acetaminophen dose was 15 mg /kg every 6 hours for 3 days intravenously. (Paracetamol Kabi TM preparation (10 mg/ml), Fresenius Kabi Laboratory). The drug was administered IV over 1 h. The ibuprofen dose was 10 mg/kg on the first day and then 5 mg/kg on the following 2 days (every 24 h). (Ibuprofen Pedea ™ preparation (5 mg/ml), Orphan Europe Laboratory). Ibuprofen was diluted in a solution of sodium chloride 0.9%, resulting in a concentration of 1 mg/ml. This drug was administered IV over 1 h.

Inclusion criteria were: preterm newborns between 25+0 – 31+6 weeks of gestational age and/or ≤1500 g of birth weight; echocardiographic diagnosis of hs-PDA within the first 2 weeks after birth; admitted to the neonatal intensive care unit of Guillermo Grant Benavente Hospital. Exclusion criteria were: major congenital malformations, fetal hydrops, complex or ductus-dependent congenital heart disease; septic shock; grade III and IV intracranial hemorrhage; renal failure with urine output <1 cc/kg/h in the previous 24 h; serum creatinine concentration >1.5 mg /dl; platelet count <50,000 $mm^3$; major bleeding (defined as the presence of massive hematuria and/or blood in tracheal aspirate), hyperbilirubinemia in the range of exchange transfusion; confirmed necrotizing enterocolitis (Bell stage >II); liver dysfunction defined as elevation of liver enzymes alanine aminotransferase (ALT) and aspartate aminotransferase (AST) over two times the upper limit of normal range (ALT 6-50 U/L and AST 35-140 U/L).

The criteria for suspending treatment with ibuprofen were: renal failure with serum creatinine greater than 2.5 mg/dl; evidence of bleeding; intestinal perforation; confirmed necrotizing enterocolitis, and for acetaminophen, evidence of acute liver failure with abrupt changes in coagulation tests not explained by consumptive coagulopathy; elevation of liver transaminases over twice the upper limit of the normal range; significant elevation of conjugated bilirubin.

During treatment with any of the two drugs, continuous monitoring of oxygen saturation, heart rate, respiratory rate, and blood pressure was performed using multi-parameter monitoring equipment. To investigate possible side effects of the drugs, the following tests were performed on each patient prior to treatment: serum creatinine, blood urea nitrogen, urine output measurement, AST, ALT, prothrombin time, activated partial thromboplastin, bilirubin,

and blood count. These tests were repeated 24 and 72 hours after the start of treatment. In addition, a brain ultrasound was performed before and after treatment to rule out intracranial hemorrhage.

Primary PDA closure was considered when it occurred shortly after the first course of pharmacological treatment. In case of persistence of the ductus, a second course of treatment was given using the same therapeutic scheme as earlier. Secondary closure was considered when it occurred after the second course of pharmacological treatment. In case of failure of ductal closure with the second course, most infants underwent surgical ligation.

## Intervention Type
Drug

## Pharmaceutical study type(s)
Comparison of effectiveness and safety between two drugs

## Phase
Not Applicable

## Drug/device/biological/vaccine name(s)
Acetaminophen, ibuprofen

## Primary outcome measure
1. Primary closure of patent ductus arteriosus measured using the percentage of ductal closure after the first course of treatment with acetaminophen or ibuprofen at 72 h after the start of the first course of treatment
2. Secondary closure of patent ductus arteriosus measured using the percentage of ductal closure after the second course of treatment with acetaminophen or ibuprofen at 72 h after the start of the second course of treatment
3. Surgical closure of patent ductus arteriosus measured using the percentage of surgical ligation performed after the second course of treatment

## Secondary outcome measures
1. Intraventricular hemorrhage measured using the percentage of intraventricular hemorrhage at the end of treatment with acetaminophen or ibuprofen
2. Pulmonary hemorrhage measured using the percentage of pulmonary hemorrhage at any time during the treatment with acetaminophen or ibuprofen
3. Early onset sepsis measured using the percentage of early-onset sepsis at any time during the treatment with acetaminophen or ibuprofen
4. Acute kidney injury measured using the percentage of acute kidney injury at any time during the treatment with acetaminophen or ibuprofen
5. Necrotizing enterocolitis measured using the percentage of necrotizing enterocolitis at any time during and after the treatment with acetaminophen or ibuprofen
6. Gastrointestinal bleeding measured using the percentage of gastrointestinal bleeding at any time during the treatment with acetaminophen or ibuprofen
7. Pneumonia measured using the percentage of pneumonia at any time during and after the treatment with acetaminophen or ibuprofen.
8. Late-onset sepsis measured using the percentage of late-onset sepsis at any time during and after the treatment with acetaminophen or ibuprofen
9. Retinopathy of prematurity measured using the percentage of retinopathy of prematurity at any time during and after the treatment with acetaminophen or ibuprofen

10. Broncopulmonary dysplasia measured using the percentage of broncopulmonary dysplasia at any time after the treatment with acetaminophen or ibuprofen
11. Primary closure of patent ductus arteriosus in patients weighing less than 1000 g measured using the percentage of ductal closure in patients weighing less than 1000 grams after the first course of treatment with acetaminophen or ibuprofen at 72 h after the start of the first course of treatment
12. Secondary closure of patent ductus arteriosus in patients weighing less than 1000 g measured using the percentage of ductal closure in patients weighing less than 1000 g after the second course of treatment with acetaminophen or ibuprofen at 72 h after the start of the second course of treatment
13. Surgical closure of patent ductus arteriosus in patients weighing less than 1000 g measured using the percentage of surgical ligation in patients weighing less than 1000 g performed after the second course of treatment
14. Primary closure of patent ductus arteriosus in patients weighing more or equal to 1000 g measured using the percentage of ductal closure in patients weighing more or equal to 1000 g after the first course of treatment with acetaminophen or ibuprofen at 72 h after the start of the first course of treatment
15. Secondary closure of patent ductus arteriosus in patients weighing more or equal to 1000 g measured using the percentage of ductal closure in patients weighing more or equal to 1000 g after the second course of treatment with acetaminophen or ibuprofen at 72 h after the start of the second course of treatment
16. Surgical closure of patent ductus arteriosus in patients weighing more or equal to 1000 g measured using the percentage of surgical ligation in patients weighing more or equal to 1000 g performed after the second course of treatment
17. Primary closure of patent ductus arteriosus in patients with a gestational age less than 28 weeks measured using the percentage of ductal closure in patients with a gestational age less than 28 weeks after the first course of treatment with acetaminophen or ibuprofen at 72 h after the start of the first course of treatment
18. Secondary closure of patent ductus arteriosus in patients with a gestational age less than 28 weeks measured using the percentage of ductal closure in patients with a gestational age less than 28 weeks after the second course of treatment with acetaminophen or ibuprofen at 72 hrs after the start of the second course of treatment
19. Surgical closure of patent ductus arteriosus in patients with a gestational age less than 28 weeks measured using the percentage of surgical ligation in patients with a gestational age less than 28 weeks performed after the second course of treatment
20. Primary closure of patent ductus arteriosus in patients with a gestational age equal to or greater than 28 weeks measured using the percentage of ductal closure in patients with a gestational age equal to or greater than 28 weeks after the first course of treatment with acetaminophen or ibuprofen at 72 h after the start of the first course of treatment
21. Secondary closure of patent ductus arteriosus in patients with a gestational age equal to or greater than 28 weeks measured using the percentage of ductal closure in patients with a gestational age equal to or greater than 28 weeks after the second course of treatment with acetaminophen or ibuprofen at 72 h after the start of the second course of treatment
22. Surgical closure of patent ductus arteriosus in patients with a gestational age equal to or greater than 28 weeks measured using the percentage of surgical ligation in patients with a gestational age equal to or greater than 28 weeks performed after the second course of treatment

## Overall study start date
01/01/2017

### Completion date
31/12/2019

# Eligibility

### Key inclusion criteria
1. Preterm newborns between 25+0 – 31+6 weeks of gestational age and/or ≤1500 g of birth weight
2. Echocardiographic diagnosis of hemodynamically significant PDA within the first 2 weeks after birth
3. Admitted to the neonatal intensive care unit of Guillermo Grant Benavente Hospital

### Participant type(s)
Patient

### Age group
Neonate

### Lower age limit
0 Days

### Upper age limit
14 Days

### Sex
Both

### Target number of participants
128

### Total final enrolment
120

### Key exclusion criteria
1. Major congenital malformations, fetal hydrops, complex or ductus-dependent congenital heart disease; septic shock
grade III and IV intracranial hemorrhage
2. Renal failure with urine output <1 cc/kg/hr in the previous 24 h
3. Serum creatinine concentration >1.5 mg/dl; platelet count <50,000 $mm^3$
4. Major bleeding (defined as the presence of massive hematuria and/or blood in tracheal aspirate), hyperbilirubinemia in the range of exchange transfusion
5. Confirmed necrotizing enterocolitis (Bell stage > II)
6. Liver dysfunction defined as elevation of liver enzymes alanine aminotransferase (ALT) and aspartate aminotransferase (AST) over two times the upper limit of normal range (ALT 6-50 U/L and AST 35-140 U/L)

### Date of first enrolment
01/06/2017

### Date of final enrolment

21/12/2019

# Locations

**Countries of recruitment**
Chile

**Study participating centre**
**Hospital Guillermo Grant Benavente**
San Martín 1436
Concepcion
Chile
4030000

# Sponsor information

**Organisation**
University of Concepción

**Sponsor details**
Janequeo corner, Av. Chacabuco S/N, Concepción, Bío Bío
Concepción
Chile
4030000
+56 (0)41 2204852
albancal@udec.cl

**Sponsor type**
University/education

**Website**
https://www.udec.cl/pexterno/

**ROR**
https://ror.org/0460jpj73

# Funder(s)

**Funder type**
Other

**Funder Name**

Investigator initiated and funded

# Results and Publications

### Publication and dissemination plan
Planned publication in a high-impact peer-reviewed journal

### Intention to publish date
01/12/2023

### Individual participant data (IPD) sharing plan
The datasets generated during and/or analysed during the current study will be available upon request to the associated investigator Andrés Marinovic (marinovic.ped@gmail.com).
The type of data that will be shared: demographic data, relevant morbidities, characteristics of the ductus arteriosus, and the treatment used in each patient. Reserving the identity of the participant.
The study information will be available from 01/01/2020.
Obtaining informed consent is considered for each patient.
For data analysis purposes, the patient's initials and the last four digits of their ID are considered. In case of requiring particular information about a study participant, the records of each one are available in the database of the Guillermo Grant Benavente Hospital.

### IPD sharing plan summary
Available on request