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Oral Paracetamol versus Oral Ibuprofen for closure of Hemodynamically Significant Patent Ductus Arteriosus in Preterm Neonates (<32 weeks): A Blinded Randomized Active Controlled Non-Inferiority Trial

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Abstract

Introduction: Hemodynamically significant patent ductus arteriosus (HS-PDA) is a common cause of mortality and morbidities in preterm infants. Existing medical therapies with Ibuprofen or Indomethacin have multiple adverse effects prohibiting the clinicians to use them in many situations. Hence, an alternative drug like paracetamol given through oral route with less side effects need to be tested against the standard drugs in an appropriate study design with least risk of bias to arrive at a conclusion

Methods and analysis: Design: Multi-site, Randomized, active controlled, non-inferiority design. **Objective:** Primary objective-to study the efficacy of oral Paracetamol for closure of HS-PDA in comparison to oral Ibuprofen in preterm neonates of <32 weeks' gestation. Pre-defined criteria would be used for HS-PDA. Randomization- web based; Allocation concealment would be ensured; the treating team, investigators, outcome assessors and the laboratory personnel would be blinded from the nature of the intervention. Echocardiography images would be coded and archived for independent review. Closure of PDA by the end of the last dose of the study drug or earlier would be the study endpoint. A sample size of 196 neonates would be enrolled with a non-inferiority margin of 15%. Both intention to treat and per protocol analysis will be done to assess the effect of contamination and protocol violations in the primary outcome.

Ethics and dissemination: Search for an effective medical therapy with least side effects is crucial. Evidence for or against oral Paracetamol in comparison to the existing therapies is thin. The trial would follow international code of ethics for clinical trial and good clinical practices. All serious adverse events would be reported in detail to the Institute Ethics Committee. A written informed consent would be obtained from one of the parent. No plan has been made for dissemination.

Registration number: CTRI/2014/08/004805

Key messages

A. What is known about this subject

Ibuprofen and Indomethacin are the current standard drugs for closure of a Hemodynamically significant PDA apart from surgical ligation. These drugs have many adverse effects involving gut, kidneys and pulmonary vasculature. Few case reports and two clinical trials have reported about use of oral paracetamol for closure of PDA

B. What this study adds

We intend to compare oral paracetamol with oral Ibuprofen to demonstrate that paracetamol is not-inferior in efficacy and safer in comparison to Ibuprofen. This would be the largest multi-site non-inferiority trial where investigators, treating team, laboratory personnel and outcome assessors would be blinded

Study background and rationale

Hemodynamically significant patent ductus arteriosus (hsPDA) is a common cause of morbidity and mortality among preterm infants (1, 2). Treatment options for the closure of hsPDA include pharmacological therapy and surgical ligation. Indomethacin and Ibuprofen, both block the conversion of arachidonic acid to prostaglandins, are the two most commonly used drugs for closure of PDA. (3, 4). The reported treatment success with ibuprofen for the management of hsPDA is between 70%-85% (5-8). Several adverse effects have been reported with such medications, including peripheral vasoconstriction, gastrointestinal bleeding and perforation, decreased platelet aggregation, hyperbilirubinemia, and renal failure (9, 10). Paracetamol (also known as acetaminophen), unlike Ibuprofen, acts on prostaglandin synthase at the peroxidase region of the enzyme (11). Paracetamol inhibition is facilitated by a decreased local concentration of hydroperoxides (12). The role of paracetamol as an alternative treatment for the closure of hsPDA has gained attention in recent years because of the potential side-effects of cyclooxygenase inhibitors (13-15). Five case series consisting of 39 patients had reported a PDA closure rate of 84-100% in neonates where treatment with indomethacin or Ibuprofen failed or were contraindicated (13, 14, 16, 17). One trial with 80 subjects concluded Oral Paracetamol is not superior to Oral Ibuprofen (18) whereas another trial with 160 subjects reported Oral Paracetamol not inferior to Oral Ibuprofen in closure of PDA (19). Considering the equivocal reports and the promise offered by paracetamol as a safer alternative, this randomized, active controlled, non-inferiority trial was planned.

Research Question

Does Oral Paracetamol administered in a dose of 15 mg per kg birth body weight per dose every 6 hourly for consecutive 3 days would lead to a rate of closure of Patent Ductus Arteriosus (PDA) not inferior by a non-inferiority margin (D) of 15 % to administering Oral Ibuprofen in a dose of 10 mg per kg birth body weight per dose on day 1 and 5 mg per kg birth body weight per dose at 24 and 48 hr from the first dose administered consecutively in preterm neonates (<32 weeks) with evidence of hemodynamically significant (HS) PDA?

Description of the study hypothesis

Null Hypothesis (H_0): $T - S \leq D$;

Alternate hypothesis (one-sided) (H_A): $T - S > D$

T – Rate of closure of PDA in the Test group that would receive Oral Paracetamol

S - Rate of closure of PDA in the Standard, active control group that would receive Oral Ibuprofen

D – Non-inferiority margin set at minus 15%

Objectives

Primary objective

To study the efficacy of Oral Paracetamol for closure of HS-PDA in comparison to Oral Ibuprofen in preterm neonates of <32 weeks gestation with evidence of HS-PDA

Secondary objectives

To compare the following between Oral Paracetamol and Oral Ibuprofen groups:

- Time to closure of PDA
- Proportion of neonates where PDA closed following a single course
- Proportion of neonates who required surgical ligation for closure of PDA
- All-cause mortality before discharge from hospital
- Proportion of neonates where the PDA reopened

- Incidence of echocardiography proven pulmonary artery hypertension
- Duration of mechanical ventilation (in days)
- Duration of any respiratory support (in days)
- Duration of need for supplemental oxygen (in days)
- Incidences of azotemia, oliguria, hepatitis with deranged liver transaminases, deranged coagulogram, intraventricular hemorrhage (any grade of severity), severe intraventricular hemorrhage (grade 3 and intra-parenchymal extension), periventricular leukomalacia necrotizing enterocolitis (all stage), necrotizing enterocolitis (definite and advanced stage as per modified Bell's staging, feed intolerance, broncho-pulmonary dysplasia and retinopathy of prematurity

Outcome measures

***Primary outcome measure*:** Closure of PDA by the end of the last dose of the study drug or earlier, irrespective of the course of the drug

Secondary outcome measures:

- Closure of PDA following a single course of study drug
- Closure of PDA following surgical ligation
- Death (due to any cause) before discharge from the hospital
- Reopening of PDA following initial closure
- Echo proven pulmonary artery hypertension
- Azotemia, oliguria, hepatitis with deranged liver transaminases, deranged coagulogram, intraventricular hemorrhage (any grade of severity), severe intraventricular hemorrhage (grade 3 and intra-parenchymal extension), periventricular leukomalacia, necrotizing enterocolitis (all stage), necrotizing enterocolitis (definite and advanced stage as per modified Bell's staging), feed intolerance, broncho-pulmonary dysplasia, and retinopathy of prematurity

Methodology

***Study design*:** Randomized, two parallel arm, active controlled, blinded, non-inferiority trial

***Study place*:** Newborn unit, Department of Pediatrics, PGIMER, Chandigarh

Eligibility criteria:

a) Inborn preterm neonates < 32 weeks' gestation

b) Presence of a hemodynamically significant PDA*

*HS-PDA is defined if any one of the below mentioned clinical/biochemical sign is present in the presence of a PDA with a trans ductal diameter of ≥ 1.6 mm (or) in the presence of any one of the below mentioned echocardiographic sign suggestive of hemodynamic significance even in the absence of any of the below mentioned clinical/biochemical sign. A screening Echo would be done in all asymptomatic neonates to detect HS-PDA and this would be timed between 48-72 hours of age in infants 29-31 weeks and in the first 48 hours for that ≤28 weeks' gestation.

Group A: Signs of significant left → right shunt:* Hyperdynamic pulsatile precordium, bounding peripheral pulses, wide pulse pressure (>25 mmHg)
Group B: Signs of systemic under-perfusion – poor peripheral pulse volume, prolonged capillary refill time, decreased urine output, deranged renal function test, metabolic acidosis, and hypotension
Group C: Signs of pulmonary over-perfusion – abnormal weight gain, increase in liver size, new onset or increase in ventilatory requirements that primarily involves PEEP, PIP and FiO2, respiratory acidosis, pulmonary crepitations, hemorrhagic pulmonary edema
*In the presence of a clinical sign that falls under Group A, a second trained neonatologist would be asked to confirm the clinical sign and the sign would be present only if both examiners concur; wide pulse pressure must be recorded on two consecutive blood pressure measurements

Echocardiographic features indicative of HS-PDA:

A trans-ductal diameter of ≥ 1.5 mm plus one of the following:

- Evidence of left atrial enlargement (LA: Ao root diameter ratio ≥1.4)
- Ductal velocity < 2 meters/sec
- Antegrade main pulmonary artery diastolic flow >20 cm/sec
- E: A ratio >1
- Isovolemic relaxation time (IVRT) ≤45 milliseconds
- Absent or reversed diastolic blood flow pattern in descending thoracic aorta

Exclusion criteria:

1. Antenatally or postnatally suspected or diagnosed structural heart disease
2. Presence of major congenital malformations
3. Contraindication for enteral feeding
4. Contraindication for administration of any one of the study drugs such as Blood Urea > 60mg/dl, serum creatinine level >1.6 mg/ dl, platelet count <60000/mm3, clinical bleeding from any site, deranged coagulogram, clinical or radiological evidence of necrotizing enterocolitis, intra-ventricular hemorrhage of moderate to severe grade severity (grade III with or without intra-parenchymal extension) or progression of intra-ventricular hemorrhage demonstrated in an earlier ultrasound, hyperbilirubinemia within 2 mg/dl from the exchange transfusion cut-off value
5. Refusal of consent

Enrollment process (Figure 1)

Consent:

One of the parents would be approached for consent to allow their newborn infant to participate in this clinical trial. The parents will be provided a detailed parent information sheet and will also receive a verbal explanation about the study. Neonates will be enrolled only after obtaining written informed consent from one of the parents. Parents would be allowed to withdraw their neonate from the study at any stage.

Intervention and comparison groups

***Intervention*:** Paracetamol oral suspension (Calpol, Glaxo Smithkline Asia Pvt Ltd) would be administered through an oro-gastric tube in a dose of 15 mg/kg/dose at 6 hourly intervals for three consecutive days. The drug would be filled in 5 ml plastic syringes and would be gently pushed through the oro-gastric tube followed by a flush of 1 ml of sterile water for injection

***Active control*:** Ibuprofen oral suspension (Ibugesic, Cipla India Ltd.) would be administered through oro-gastric tubes in a dose of 10 mg/kg/dose followed by 5 mg/kg/dose after 24 and 48 hours from the first dose. A similar drug administration technique would be followed as stated above

Allocation process

Web based random allocation would be done within each of the three strata (<28 weeks, 28-29 and 30-31 weeks) (http://www.randomization.com). A block randomization would be done with blocks of variable sizes within each stratum. Separate personnel who are not involved in any aspect of the trial would do the random allocation.

Allocation concealment and blinding

The drugs would be prepared and dispensed by the clinical pharmacy department of the Institute. The drugs would be dispensed in 5 ml volumes in separate vials as per the group of allocations. Allocation concealment would be ensured by serially numbering the vials with a randomly generated code number corresponding to the sequence of allocation. The drugs would be prepared to have a similar color, flavor, and viscosity to prevent identification of the study drug

and would be dispensed on opaque plastic vials. The blinding process would be tested by administering the dispensed drugs to adult volunteers to assess whether they can differentiate the drugs based on the color, flavor, taste and viscosity of the preparations. To avoid recognizing the study drug due to difference in their respective dosage and frequency schedules, the concentration of the drugs would be modified in such a way that administering equal volume of the drug at a time point would ensure appropriate dosing of that drug for that time point. The final concentration that would be achieved would be 1ml=15 mg for paracetamol and 1ml=10 mg for Ibuprofen. Moreover, as once daily schedule would be followed for Ibuprofen, a similar resembling placebo (inert agent) would be used to complete a sham 6 hourly dosing schedule in case of the Ibuprofen group. This process would be ensured by having a set of 24 vials (12 vials for first course and 12 more for the second course) for each enrolled neonate with the vials clearly marked with the code number, sequence of enrollment, and the day of therapy on the vial label. For the second course, vials marked day 4, 5, and 6 would be used. No drug from an already opened vial would be reused for the next day therapy. This whole process would keep the treating team, investigators, outcome assessors and the laboratory personnel blinded from the nature of the intervention. Moreover, the outcome assessors would be further blinded by coding the echo images stored in the system for assessment of ductal closure.

Determination of ductus arteriosus status by echocardiography (Figure 2 & 3):

Daily echocardiographic assessments would be done till completion of the course or till the closure of the PDA, whichever is earlier. A PDA would be considered as closed if there is no demonstrable open ductus and the color Doppler demonstrates no flow across the ductus arteriosus region. After 24 hours from the completion or earlier in case clinical signs appear, a repeat echocardiogram would be done to assess for reopening of PDA. The echocardiogram images and clips would be code numbered and archived for review VS or SS. SD will maintain the key to the code numbers.

Technique of transthoracic echocardiography

The Echocardiographic assessments will be done using a SonoSite MicroMaxx Portable Ultrasound Machine (Fujifilm Sonosite Inc. Bothell, WA 98021, USA); Philips CX-50 machine (Philips Healthcare, Massachusetts, USA) in site 2 and Esaote MyLab 5 (Esaote Inc. Genova, Italy) in site 3. A cardiac probe of 8-12 MHz frequency will be utilized for the study.

Before the procedure, the probe head will be cleaned and cold-disinfected with 2% glutaraldehyde solution. Three standard views would be optimized for visualization of the ductus arteriosus – subxiphoid, high parasternal (ductal) and aortic arch (suprasternal) views. Presence of ductus in a 2-D would always be crosschecked using a color Doppler superimposition. Transductal diameter would be measured preferably in a 2-D in a high parasternal cut. To maintain uniformity, the diameter measurement will be done at the narrowest point by 2-D imaging, which is usually at the pulmonary end of the ductus arteriosus, where it constricts first. Color Doppler mapping would be used to visualize the direction of shunt blood flow. Ductal velocity would be assessed using pulsed wave Doppler (PWD) positioned at the pulmonary end of the ductus. Similarly, PWD would be used to assess the antegrade flow in diastole in the main pulmonary artery (MPA). M-mode would be used to measure the left atrial: aortic root diameter ratio. PWD with range gate would be placed transmitrally for E: A ratio and between the mitral and aortic valves for IVRT. Left ventricular output (LVO), right ventricular output (RVO) and superior vena cava (SVC) flow would be measured using the formula: [VTI (cm) x π x $(D/2)^2$ x heart rate]/birth weight (kg). Velocity Time Integral (VTI) will be calculated based on PWD across the left ventricle outflow tract for LVO, right ventricular outflow tract for RVO, and SVC for SVC flow. The descending aorta would be visualized in the suprasternal view and using Continuous Wave (CW) Doppler the flow direction in diastole would be calculated for aortic run-off.

Training of the principal investigator: The principal investigator (PI) in each site would be formally evaluated over a period of 1 month preceded by a hands-on training session. During the training session, PI would be trained by one of the co-investigators who have experience in performing neonatal functional echocardiographic assessments (VS and SS). During the evaluation period, the PI would record 50 images and video clips from 50 different neonates with 20% of them being normal neonates. VS or SS would review these images for correctness of image acquisition and diagnosis. The PI would be considered trained to perform independent Echocardiography for the research purpose when he gets >90% of the images correct. At the end of evaluation, 10 out of 50 images would be repeated by co investigators VS or SS to check for inter-observer variability.

Sample size estimation and statistical analysis:

The observed rate of PDA closure by oral Ibuprofen was 85% (20). Assuming an equal rate of closure for oral paracetamol with a non-inferiority margin of 15%, one sided alpha error of 5% and power of 90%, 196 neonates would be required in this trial. The primary outcome (binary) of rate of closure of PDA will be compared between the study groups by calculating the relative risk and risk difference and would be expressed as 95% C.I. Baseline variables would be compared between the study groups using Chi-square test for categorical variables and student 't' test or an appropriate nonparametric test for numerical variables. Time to closure of PDA would be compared by a Kaplan-Meier curve and significance will be tested by log rank test. Both intention to treat and per protocol analysis will be done to assess the effect of contamination and protocol violations on the primary outcome. Apart from hypothesis testing for non-inferiority using the non-inferiority margin assumed, the 95% CI of the probability of closure of PDA would be marked to establish or reject non-inferiority of Paracetamol in comparison to oral ibuprofen. A 'p' value of 0.05 would be considered significant. IBM-SPSS v.20 will be used for data entry and statistical analysis.

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Figure 1: Study flow as per the CONSORT recommendations

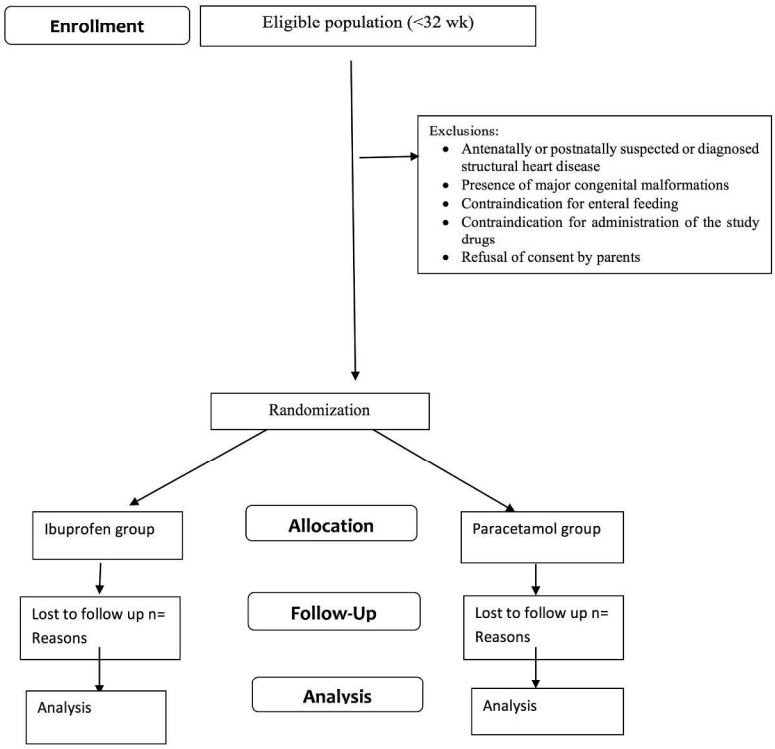

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Figure 2: Operational flow and time line of the study

Step 1: Eligible neonate (<32 weeks with clinical signs suggestive of HS-PDA and in the first 2 weeks of age or directly screened for Echo proven HS-PDA) identified and first Echo done (Zero-hour echo)

Step 2: Structural abnormality of heart ruled out by the investigators (even suspicion of a structural heart disease would make them not eligible)

Step 3: Exclusion criteria applied (certain investigations like platelet count and renal function tests – sent and results acquired within the next 6 hours)

Step 4: Randomized to one of the study groups (time of randomization in hours and the age at diagnosis - age at randomization difference noted)

Step 5: Study drug administered as per the random allocation (the age at intervention and the randomization – intervention interval noted)

Step 6: Repeat echo's (Echo 1, 2, and 3) done at 24 ± 4 hours' interval) on 1st, 2nd, and 3rd day drug dose for closure of PDA

Step 7: If Ductus still open on Echo 3, repeat course of the same study drug of same duration would be started and the Echo would be repeated as per the first course schedule

Step 8: The Ductus would be finally labeled as failed to close based on Echo 6, which would be done at the end of the last dose of the second course of the study drug

Note: The first course would be completed even though a ductal closure is documented earlier. However, if a baby required a second course, the drug would be stopped the moment a ductal closure has been documented at any point during the daily Echocardiographic assessments

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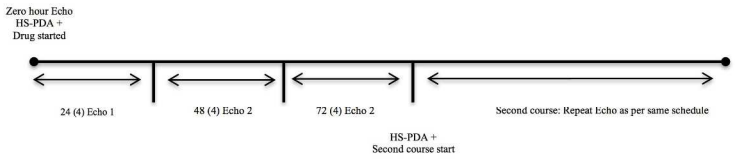
Figure 3: Time line of assessments by Bedside Echocardiography



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Abstract

Introduction: Hemodynamically significant patent ductus arteriosus (HS-PDA) is a common cause of mortality and morbidities in preterm infants. Existing medical therapies with Ibuprofen or Indomethacin have multiple adverse effects. Hence, an alternative drug like paracetamol given through oral route with less side effects need to be tested in an appropriate study design with least risk of bias to arrive at a conclusion

Methods and analysis: Multi-site, Randomized, active controlled, non-inferiority design. Primary objective-to study the efficacy of oral paracetamol for closure of HS-PDA in comparison to oral ibuprofen in preterm neonates of <32 weeks' gestation. Randomization- web based; Allocation concealment would be done; the treating team, investigators, outcome assessors and laboratory personnel would be blinded from the intervention. Echocardiography images would be coded for independent review. Closure of PDA by the end of last dose of study drug or earlier would be the study endpoint. A sample size of 196 neonates would be enrolled with a non-inferiority margin of 15%. Both intention to treat and per protocol analysis will be done to assess the effect of contamination and protocol violations in the primary outcome.

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Key messages

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B. What this study adds

We intend to compare oral paracetamol with oral ibuprofen to demonstrate that paracetamol is not-inferior in efficacy and safer in comparison to ibuprofen. This would be the largest multi-site, non-inferiority trial where investigators, treating team, laboratory personnel and outcome assessors would be blinded to the intervention

Study background and rationale

Hemodynamically significant patent ductus arteriosus (hsPDA) is a common cause of morbidity and mortality in preterm neonates (1, 2). Treatment options for the closure of hsPDA include pharmacological therapy and surgical ligation. Indomethacin and Ibuprofen, both inhibit the conversion of arachidonic acid to prostaglandins, are the two most commonly used drugs for closure of PDA (3, 4). Ibuprofen has been reported to successfully close hsPDA in 70-85% cases (5-8). However, several serious adverse effects have been reported with both Indomethacin and Ibuprofen which includes intense peripheral vasoconstriction, gastrointestinal bleeding and perforation, decreased platelet aggregation, hyperbilirubinemia, and renal failure (9, 10). Paracetamol (also known as acetaminophen), unlike Ibuprofen, acts on prostaglandin synthase at the peroxidase region of the enzyme (11). Paracetamol mediated inhibition of the peroxidase region enzyme was reported to be further facilitated by decreased local concentration of hydroperoxides (12). The role of paracetamol as an alternative treatment for closure of hsPDA has gained attention in recent years because of its superior safety profile in comparison to the cyclooxygenase inhibitors (13-15). Five case series together consisting of 39 neonates who received paracetamol for significant PDA (where Indomethacin and Ibuprofen were contraindicated) had reported a closure rate of 84-100% (13, 14, 16, 17). A clinical trial comparing oral paracetamol with oral Ibuprofen in 80 preterm neonates concluded that oral paracetamol was not superior to oral Ibuprofen (18) whereas another trial with 160 preterm neonates reported that oral paracetamol was not inferior to oral Ibuprofen in closure of PDA (19). A Cochrane database systematic review of two low quality unmasked studies that enrolled 250 infants (above two studies) showed no significant difference between treatment with oral paracetamol versus oral ibuprofen for failure of ductal closure after the first course of drug administration (typical relative risk (RR) 0.90, 95% confidence interval (CI) 0.67 to 1.22) (20). There were also no significant differences between the paracetamol and the ibuprofen groups in the secondary outcomes except for ‘duration for need of supplemental oxygen’ and for hyperbilirubinemia, both in favor of paracetamol. However, both the studies included were graded down by the review group as low in quality using the GRADE process. Another recent systematic review of sixteen studies (2 randomized controlled trials and 14 uncontrolled studies) concluded that the efficacy and safety of paracetamol appear to be comparable with those of ibuprofen. However, the authors cautioned about the non-optimal quality of the studies analyzed

and the limited number of neonates treated with paracetamol so far and advised for additional well designed studies to support the use of paracetamol for PDA in current clinical practice (21). A recent report has reinforced the long-term neurodevelopmental safety of paracetamol in comparison to ibuprofen in 80 preterm neonates (22). Considering the equivocal reports published until now and the promise offered by paracetamol as a safer alternative, this randomized, active controlled, masked, non-inferiority trial was planned.

Research Question

Does oral paracetamol administered in a dose of 15 mg per kg per dose every 6 hourly for 3 consecutive days would be associated with a rate of closure of Patent Ductus Arteriosus (PDA) not inferior by a non-inferiority margin (D) of 15 % in comparison to oral ibuprofen in a dose of 10 mg per kg per dose on day 1 and 5 mg per kg per dose at 24 and 48 hours from the first dose in preterm neonates (<32 weeks) with evidence of hemodynamically significant (HS) PDA?

Description of the study hypothesis

Null Hypothesis (H_0): $T - S \leq D$;

Alternate hypothesis (one-sided) (H_A): $T - S > D$

T – Rate of closure of PDA in the test group that would receive oral paracetamol

S - Rate of closure of PDA in the standard, active control group that would receive oral ibuprofen

D – Non-inferiority margin set at minus 15%

Objectives

Primary objective

To study the efficacy of Oral Paracetamol for closure of HS-PDA in comparison to Oral Ibuprofen in preterm neonates of <32 weeks' gestation with evidence of HS-PDA

Secondary objectives

To compare the following between Oral Paracetamol and Oral Ibuprofen groups:

- Time to closure of PDA
- Proportion of neonates where PDA closed following a single course
- Proportion of neonates who required surgical ligation for closure of PDA
- All-cause mortality before discharge from hospital
- Proportion of neonates where the PDA reopened
- Incidence of echocardiography proven pulmonary artery hypertension

- Duration of mechanical ventilation (in days)
- Duration of any respiratory support (in days)
- Duration of need for supplemental oxygen (in days)
- Incidences of azotemia, oliguria, hepatitis with deranged liver transaminases, deranged coagulogram, intraventricular hemorrhage (any grade of severity), severe intraventricular hemorrhage (grade 3 and intra-parenchymal extension), periventricular leukomalacia necrotizing enterocolitis (all stage), necrotizing enterocolitis (definite and advanced stage as per modified Bell's staging, feed intolerance, broncho-pulmonary dysplasia and retinopathy of prematurity

Outcome measures

***Primary outcome measure*:** Closure of PDA by the end of the last dose of the study drug or earlier, irrespective of the course of the drug

Secondary outcome measures:

- Closure of PDA following a single course of study drug
- Closure of PDA following surgical ligation
- Death (due to any cause) before discharge from the hospital
- Reopening of PDA following initial closure
- Echo proven pulmonary artery hypertension
- Azotemia, oliguria, hepatitis with deranged liver transaminases, deranged coagulogram, intraventricular hemorrhage (any grade of severity), severe intraventricular hemorrhage (grade 3 and intra-parenchymal extension), periventricular leukomalacia, necrotizing enterocolitis (all stage), necrotizing enterocolitis (definite and advanced stage as per modified Bell's staging), feed intolerance, broncho-pulmonary dysplasia, and retinopathy of prematurity

Methodology

***Study design*:** Randomized, two parallel arm, active controlled, blinded, non-inferiority trial

***Study place*:** Newborn unit, Department of Pediatrics, PGIMER, Chandigarh

Eligibility criteria:

a) Inborn preterm neonates < 32 weeks' gestation

b) Presence of a hemodynamically significant PDA*

*HS-PDA is defined if any one of the below mentioned clinical/biochemical sign is present in the presence of a PDA with a trans ductal diameter of ≥ 1.6 mm (or) in the presence of any one of the below mentioned echocardiographic sign suggestive of hemodynamic significance even in the absence of any of the below mentioned clinical/biochemical sign. A screening Echo would be done in all asymptomatic neonates to detect HS-PDA and this would be timed between 48-72 hours of age in infants 29-31 weeks and in the first 48 hours for that ≤28 weeks' gestation.

Group A: Signs of significant left → right shunt:* Hyperdynamic pulsatile precordium, bounding peripheral pulses, wide pulse pressure (>25 mmHg)
Group B: Signs of systemic under-perfusion – poor peripheral pulse volume, prolonged capillary refill time, decreased urine output, deranged renal function test, metabolic acidosis, and hypotension
Group C: Signs of pulmonary over-perfusion – abnormal weight gain, increase in liver size, new onset or increase in ventilatory requirements that primarily involves PEEP, PIP and FiO2, respiratory acidosis, pulmonary crepitations, hemorrhagic pulmonary edema
*In the presence of a clinical sign that falls under Group A, a second trained neonatologist would be asked to confirm the clinical sign and the sign would be present only if both examiners concur; wide pulse pressure must be recorded on two consecutive blood pressure measurements

Echocardiographic features indicative of HS-PDA:

A trans-ductal diameter of ≥ 1.5 mm plus one of the following:

- Evidence of left atrial enlargement (LA: Ao root diameter ratio ≥1.4)
- Ductal velocity < 2 meters/sec
- Antegrade main pulmonary artery diastolic flow >20 cm/sec
- E: A ratio >1
- Isovolemic relaxation time (IVRT) ≤45 milliseconds
- Absent or reversed diastolic blood flow pattern in descending thoracic aorta

Exclusion criteria:

1. Antenatally or postnatally suspected or diagnosed structural heart disease
2. Presence of major congenital malformations
3. Contraindication for enteral feeding
4. Contraindication for administration of any one of the study drugs such as Blood Urea > 60mg/dl, serum creatinine level >1.6 mg/ dl, platelet count <60000/mm3, clinical bleeding from any site, deranged coagulogram, clinical or radiological evidence of necrotizing enterocolitis, intra-ventricular hemorrhage of moderate to severe grade severity (grade III with or without intra-parenchymal extension) or progression of intra-ventricular hemorrhage demonstrated in an earlier ultrasound, hyperbilirubinemia within 2 mg/dl from the exchange transfusion cut-off value
5. Refusal of consent

Enrollment process (Figure 1)

Consent:

One of the parents would be approached for consent to allow their newborn infant to participate in this clinical trial. The parents will be provided a detailed parent information sheet and will also receive a verbal explanation about the study. Neonates will be enrolled only after obtaining written informed consent from one of the parents. Parents would be allowed to withdraw their neonate from the study at any stage.

Intervention and comparison groups

***Intervention*:** Paracetamol oral suspension (Calpol, Glaxo Smithkline Asia Pvt Ltd) would be administered through an oro-gastric tube in a dose of 15 mg/kg/dose at 6 hourly intervals for three consecutive days. The drug would be filled in 5 ml plastic syringes and would be gently pushed through the oro-gastric tube followed by a flush of 1 ml of sterile water for injection

***Active control*:** Ibuprofen oral suspension (Ibugesic, Cipla India Ltd.) would be administered through oro-gastric tubes in a dose of 10 mg/kg/dose followed by 5 mg/kg/dose after 24 and 48 hours from the first dose. A similar drug administration technique would be followed as stated above

Allocation process

Web based random allocation would be done within each of the three strata (<28 weeks, 28-29 and 30-31 weeks) (http://www.randomization.com). A block randomization would be done with blocks of variable sizes within each stratum. Separate personnel who are not involved in any aspect of the trial would do the random allocation.

Allocation concealment and blinding

The drugs would be prepared and dispensed by the clinical pharmacy department of the Institute. The drugs would be dispensed in 5 ml volumes in separate vials as per the group of allocations. Allocation concealment would be ensured by serially numbering the vials with a randomly generated code number corresponding to the sequence of allocation. The drugs would be prepared to have a similar color, flavor, and viscosity to prevent identification of the study drug and would be dispensed on opaque plastic vials. The blinding process would be tested by administering the dispensed drugs to adult volunteers to assess whether they can differentiate the

drugs based on the color, flavor, taste and viscosity of the preparations. To avoid recognizing the study drug due to difference in their respective dosage and frequency schedules, the concentration of the drugs would be modified in such a way that administering equal volume of the drug at a time point would ensure appropriate dosing of that drug for that time point. The final concentration that would be achieved would be 1ml=15 mg for paracetamol and 1ml=10 mg for Ibuprofen. Moreover, as once daily schedule would be followed for Ibuprofen, a similar resembling placebo (inert agent) would be used to complete a sham 6 hourly dosing schedule in case of the Ibuprofen group. This process would be ensured by having a set of 24 vials (12 vials for first course and 12 more for the second course) for each enrolled neonate with the vials clearly marked with the code number, sequence of enrollment, and the day of therapy on the vial label. For the second course, vials marked day 4, 5, and 6 would be used. No drug from an already opened vial would be reused for the next day therapy. This whole process would keep the treating team, investigators, outcome assessors and the laboratory personnel blinded from the nature of the intervention. Moreover, the outcome assessors would be further blinded by coding the echo images stored in the system for assessment of ductal closure.

Determination of ductus arteriosus status by echocardiography (Figure 2 & 3):

Daily echocardiographic assessments would be done till completion of the course or till the closure of the PDA, whichever is earlier. A PDA would be considered as closed if there is no demonstrable open ductus and the color Doppler demonstrates no flow across the ductus arteriosus region. After 24 hours from the completion or earlier in case clinical signs appear, a repeat echocardiogram would be done to assess for reopening of PDA. The echocardiogram images and clips would be code numbered and archived for review VS or SS. SD will maintain the key to the code numbers.

Technique of transthoracic echocardiography

The Echocardiographic assessments will be done using a SonoSite MicroMaxx Portable Ultrasound Machine (Fujifilm Sonosite Inc. Bothell, WA 98021, USA); Philips CX-50 machine (Philips Healthcare, Massachusetts, USA) in site 2 and Esaote MyLab 5 (Esaote Inc. Genova, Italy) in site 3. A cardiac probe of 8-12 MHz frequency will be utilized for the study. Before the procedure, the probe head will be cleaned and cold-disinfected with 2% glutaraldehyde solution. Three standard views would be optimized for visualization of the ductus arteriosus – subxiphoid, high parasternal (ductal) and aortic arch (suprasternal) views.

Presence of ductus in a 2-D would always be crosschecked using a color Doppler superimposition. Transductal diameter would be measured preferably in a 2-D in a high parasternal cut. To maintain uniformity, the diameter measurement will be done at the narrowest point by 2-D imaging, which is usually at the pulmonary end of the ductus arteriosus, where it constricts first. Color Doppler mapping would be used to visualize the direction of shunt blood flow. Ductal velocity would be assessed using pulsed wave Doppler (PWD) positioned at the pulmonary end of the ductus. Similarly, PWD would be used to assess the antegrade flow in diastole in the main pulmonary artery (MPA). M-mode would be used to measure the left atrial: aortic root diameter ratio. PWD with range gate would be placed transmitrally for E: A ratio and between the mitral and aortic valves for IVRT. Left ventricular output (LVO), right ventricular output (RVO) and superior vena cava (SVC) flow would be measured using the formula: [VTI (cm) x π x $(D/2)^2$ x heart rate]/birth weight (kg). Velocity Time Integral (VTI) will be calculated based on PWD across the left ventricle outflow tract for LVO, right ventricular outflow tract for RVO, and SVC for SVC flow. The descending aorta would be visualized in the suprasternal view and using Continuous Wave (CW) Doppler the flow direction in diastole would be calculated for aortic run-off.

Training of the principal investigator: The principal investigator (PI) in each site would be formally evaluated over a period of 1 month preceded by a hands-on training session. During the training session, PI would be trained by one of the co-investigators who have experience in performing neonatal functional echocardiographic assessments (VS and SS). During the evaluation period, the PI would record 50 images and video clips from 50 different neonates with 20% of them being normal neonates. VS or SS would review these images for correctness of image acquisition and diagnosis. The PI would be considered trained to perform independent Echocardiography for the research purpose when he gets >90% of the images correct. At the end of evaluation, 10 out of 50 images would be repeated by co investigators VS or SS to check for inter-observer variability.

Sample size estimation and statistical analysis:

The observed rate of PDA closure by oral Ibuprofen was 85% (23). Assuming an equal rate of closure for oral paracetamol with a non-inferiority margin of 15%, one sided alpha error of 5% and power of 90%, 196 neonates would be required in this trial. The primary outcome (binary) of rate of closure of PDA will be compared between the study groups by calculating the relative risk and risk difference and would be expressed as 95% C.I. Baseline variables would be compared between the study groups using Chi-square test for categorical variables and student 't' test or an appropriate nonparametric test for numerical variables. Time to closure of PDA would be compared by a Kaplan-Meier curve and significance will be tested by log rank test. Both intention to treat and per protocol analysis will be done to assess the effect of contamination and protocol violations on the primary outcome. Apart from hypothesis testing for non-inferiority using the non-inferiority margin assumed, the 95% CI of the probability of closure of PDA would be marked to establish or reject non-inferiority of Paracetamol in comparison to oral ibuprofen. A 'p' value of 0.05 would be considered significant. IBM-SPSS v.20 will be used for data entry and statistical analysis.

Ethics and dissemination:

The trial would follow international code of ethics for clinical trial and good clinical practices (GCP). The trial protocol has been approved by the Institute Ethics Committee of all the three centres. All serious adverse events would be reported in detail to the Institute Ethics Committee. A written informed consent would be obtained from one of the parent. No plan has been made for dissemination.

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Authors' contributions:

Ashutosh Kumar (AK) assisted in designing and planning the study and wrote the first draft of the protocol
Venkataseshan Sundaram (VS) conceived the idea, designed the trial and critically edited and approved the manuscript.
Tejopratap Oleti (TO) assisted in planning the study and critically edited and approved the manuscript
Srinivas Murki (SM) assisted in designing and planning the study and critically edited and approved the manuscript
Arun Krishna (ArK) assisted in planning the study and wrote the first draft of the protocol
Mangalabharathi Sundaram (MS) assisted in designing and planning the study and critically edited and approved the manuscript
Shivsajan Saini (SS) assisted in planning the study and critically edited and approved the manuscript
Sourabh Dutta (SD) assisted in designing and planning the study and critically edited and approved the manuscript

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Data sharing: No additional unpublished data is available. Data that is being collected can be accessed by one of the site investigator (VS, SM and MS) and they should be preferably contacted through the corresponding author to obtain the data.

Figure 1: Study flow as per the CONSORT recommendations

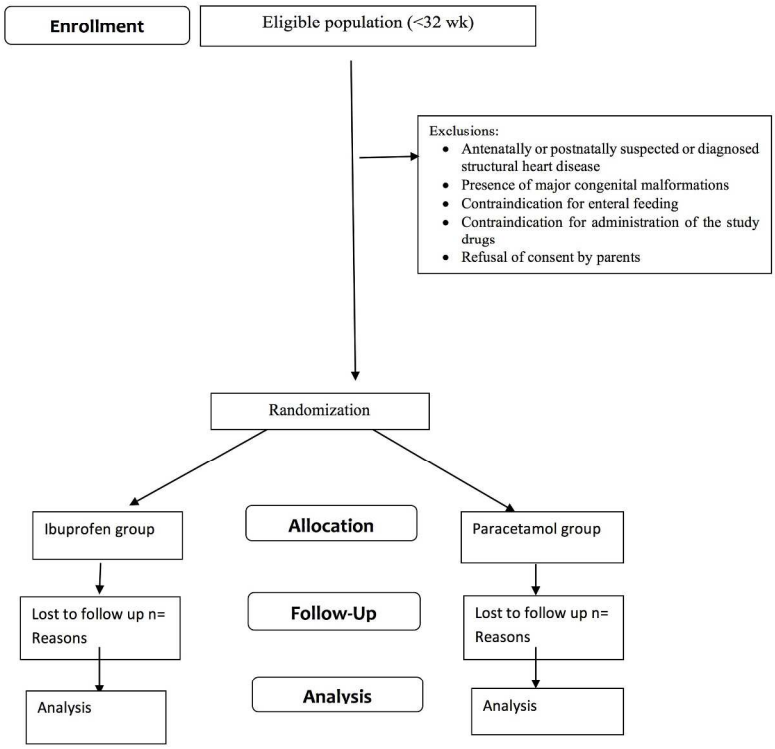

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Figure 2: Operational flow and time line of the study

Step 1: Eligible neonate (<32 weeks with clinical signs suggestive of HS-PDA and in the first 2 weeks of age or directly screened for Echo proven HS-PDA) identified and first Echo done (Zero-hour echo)

Step 2: Structural abnormality of heart ruled out by the investigators (even suspicion of a structural heart disease would make them not eligible)

Step 3: Exclusion criteria applied (certain investigations like platelet count and renal function tests – sent and results acquired within the next 6 hours)

Step 4: Randomized to one of the study groups (time of randomization in hours and the age at diagnosis - age at randomization difference noted)

Step 5: Study drug administered as per the random allocation (the age at intervention and the randomization – intervention interval noted)

Step 6: Repeat echo's (Echo 1, 2, and 3) done at 24 ± 4 hours' interval) on 1st, 2nd, and 3rd day drug dose for closure of PDA

Step 7: If Ductus still open on Echo 3, repeat course of the same study drug of same duration would be started and the Echo would be repeated as per the first course schedule

Step 8: The Ductus would be finally labeled as failed to close based on Echo 6, which would be done at the end of the last dose of the second course of the study drug

Note: The first course would be completed even though a ductal closure is documented earlier. However, if a baby required a second course, the drug would be stopped the moment a ductal closure has been documented at any point during the daily Echocardiographic assessments

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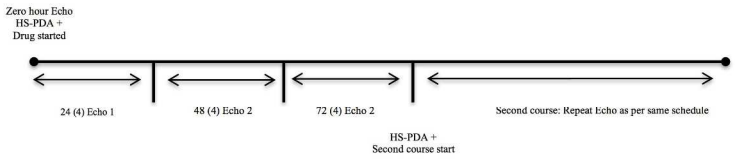
Figure 3: Time line of assessments by Bedside Echocardiography



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