



BMJ Open iPAPP: study protocol for a multicentre randomised controlled trial comparing safety and efficacy of intravenous paracetamol and indomethacin for the treatment of patent ductus arteriosus in preterm infants

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ABSTRACT

Introduction Patent ductus arteriosus (PDA) causes severe morbidity in premature infants. Although the use of indomethacin is the standard therapy for PDA, it is sometimes not applicable because of its adverse effects, such as renal and platelet dysfunctions. Paracetamol has emerged as an alternative to indomethacin owing to its excellent safety profile in infants. Of the recently reported case series and clinical trials on the use of paracetamol for PDA, there are few reports in Japan on paracetamol use in preterm infants. Furthermore, indications for the use of paracetamol for PDA have not been approved for use in PDA. While the safety of intravenous paracetamol therapy in case series of preterm infants treated for haemodynamically significant PDA (hsPDA) has been reported, studies which were conducted to compare paracetamol to indomethacin are limited. We, therefore, intend to investigate the hypothesis that intravenous administration of paracetamol has superior safety over indomethacin.

Methods and analysis Multicentre open-label randomised controlled trial for intravenous administration of paracetamol for PDA in preterm infants. The inclusion criteria are (1) hsPDA, (2) gestational age from 24 to 34 weeks and birth weight (BW) from 500 to 2000 g, (3) enrolment between 24 hours and 7 days from birth and (4) obtaining parental consent. The primary outcome is renal dysfunction within 48 hours from the last dose of the study drug. Enrolled patients fulfilling all the inclusion criteria are randomly allocated to either intravenous paracetamol or intravenous indomethacin. This trial requires 110 patients.

Ethics and dissemination The clinical trial would follow Japan's Clinical Trials Act. The trial protocol was approved by the Clinical Research Review Board of Saitama Medical University (approval number: 222001). A written informed consent would be obtained from one of the parents. The results are expected to be published in a scientific journal.

Trial registration number jRCTs031220386.

Protocol version 31 March 2022, version 1.0.

STRENGTHS AND LIMITATIONS OF THIS STUDY

- ⇒ This randomised controlled trial aims to determine whether, in comparison with indomethacin, paracetamol can reduce the incidence of renal dysfunction in infants requiring intervention for patent ductus arteriosus.
- ⇒ The primary outcome is renal dysfunction, which is defined as serum creatinine level ≥ 0.3 mg/dL or a 1.5-fold increase from baseline or urine output < 1 mL/kg/H (24 hours) within 48 hours from the last dose of the study drug.
- ⇒ Important pharmacological and safety data on the use of paracetamol in preterm infants will be collected.
- ⇒ The open-label trial design allows clinicians and care providers to be aware of treatment allocations that may lead to bias in estimated treatment effects.

INTRODUCTION

Background

Patent ductus arteriosus (PDA) is a condition in which the fetal ductus arteriosus (DA) remains unclosed for a certain period after birth, leading to heart failure due to increased cardiac stress. PDA is also associated with a longer duration of endotracheal mechanical ventilation, higher rates of death, bronchopulmonary dysplasia, necrotising enterocolitis, renal failure, intracranial haemorrhage and cerebral palsy.¹⁻⁶ The more immature the infant at birth, the less likely it is to close spontaneously and the earlier it progresses to heart failure and other prematurity-related morbidities, requiring intensive care and medical treatment, and surgery. PDA occurs in 30% of very low birthweight infants (VLBWIs, < 1500 g),¹ and 5000 VLBWIs are

born annually in Japan,⁷ thus the estimated incidence of 1500 VLBWIs per year.

Cyclooxygenase (COX) inhibitors such as indomethacin are drugs used for the treatment of PDA. However, despite being standard treatments for PDA, COX inhibitors are associated with side effects such as renal and platelet dysfunction, and approximately 30% of patients fail to respond to treatment.⁸⁻⁹ Recently, ibuprofen, another type of COX inhibitor, has been approved in Japan for treatment of patients with symptomatic PDA who do not respond to conservative therapy, thus raising expectations for fewer side effects; however, it causes renal dysfunction and exacerbates jaundice, similar to indomethacin and contraindications remain unchanged.⁸⁻¹¹

Rationale

Paracetamol has recently been suggested as an alternative therapy for the treatment of PDA. Paracetamol is a drug with an excellent safety profile in infants when used to treat mild to moderate pain and fever. Few cases of adverse events in neonates that were treated with paracetamol have been reported,¹² and according to a Cochran review updated in 2020, paracetamol is more effective than placebo or no treatment for PDA (low-quality evidence), has the same therapeutic effect as COX inhibitors (moderate-quality evidence) and has fewer side effects such as renal dysfunction (low-quality evidence).¹⁰ In addition, although paracetamol is an unapproved drug, it is listed in guidelines in the UK, Turkey and other countries, along with the dose and route of administration. Several ongoing clinical trials have been registered, but few have reported the use of paracetamol in Japan; it has not yet been approved for this indication by the Japanese regulatory agency (Pharmaceuticals and Medical Devices Agency).

We conducted a pilot study on a small number of patients to confirm the safety of PDA treatment with paracetamol in Japan. Paracetamol at 7.5 mg/kg or 15 mg/kg was administered to PDA patients who were refractory to or contraindicated by existing drug therapies. In this pilot study, three patients were administered 7.5 mg/kg and subsequently required surgical closure, but no adverse events were observed.¹³ In contrast, 16 patients were administered 15 mg/kg and 9 of them did not require surgery, thereby indicating the drug's efficacy.¹⁴ The neonates who received paracetamol at 15 mg/kg did not present any adverse events as well.

Evidence summary

Online supplemental table 1 summarises the existing randomised clinical trials (RCTs) published since January 2012 that compared paracetamol and indomethacin.⁸⁻¹⁵⁻¹⁷ Based on the data obtained by these trials, paracetamol appears to have promising clinical results with a low rate of renal dysfunction, although there have been no RCTs that investigated the rate of renal dysfunction as a primary outcome. The doses were paracetamol 15 mg/kg every 6 hours and indomethacin 0.2 mg/kg, followed by

0.1–0.25 mg/kg. Primary outcomes were the rate of PDA closure after the course of treatment or successful PDA treatment (no longer meeting echocardiogram inclusion criteria for haemodynamically significant PDA (hsPDA)). Secondary outcomes included renal impairments including renal dysfunction (presence of either oliguria within 6 hours or serum creatinine levels more than twice the age-appropriate norms), decreased urine output and increased levels of blood urea nitrogen (BUN) or creatinine. Davidson *et al* reported that there was no statistical difference in oliguria and elevation in creatinine levels between patients treated with intravenous paracetamol and intravenous indomethacin.¹⁶ In contrast, in trials by El-Mashad *et al* and Meena *et al*, BUN and creatinine levels significantly increased after indomethacin administration, but not after the treatment with paracetamol.⁸⁻¹⁷ Moreover, El-Mashad *et al* reported significantly decreased urine output in the indomethacin group after treatment.⁸

Aim

This multicentre, open-label, two parallel-arms, RCT aims to verify that intravenous paracetamol therapy for hsPDA in premature infants has a lower incidence of renal dysfunction than the standard treatment of intravenous indomethacin.

Hypothesis

We hypothesise that the use of intravenous paracetamol is associated with a lower proportion of renal dysfunction in preterm infants <35 weeks of gestation with hsPDA as compared with the use of intravenous indomethacin.

METHODS AND ANALYSIS

Study design

This multicentre, open-label, two parallel arms, RCT will be conducted for 3 years (October 2022 to October 2025), stratified by gestational age (GA) and presence or absence of indomethacin prophylaxis for the prevention of intraventricular haemorrhage (IVH). A trial synopsis (online supplemental table 2) and flow chart (figure 1) summarise the trial design.

Study setting

This study will be conducted at 17 centres in Japan (figure 2).

Eligibility criteria

► Presence of a hsPDA*.

*hsPDA is considered if two of the following echocardiographic signs are present: (1) left-to-right shunt and (2) the presence of at least two of the following echocardiographic signs suggestive of haemodynamic significance: internal DA diameter >1.5 mm; left atrium-to-aorta (LA/Ao) ratio >1.5; or reverse diastolic flow in the superior mesenteric artery or anterior cerebral artery. A screening echo would be performed in all preterm infants to detect hsPDA. This would be timed between 24 hours to 7 days of age.

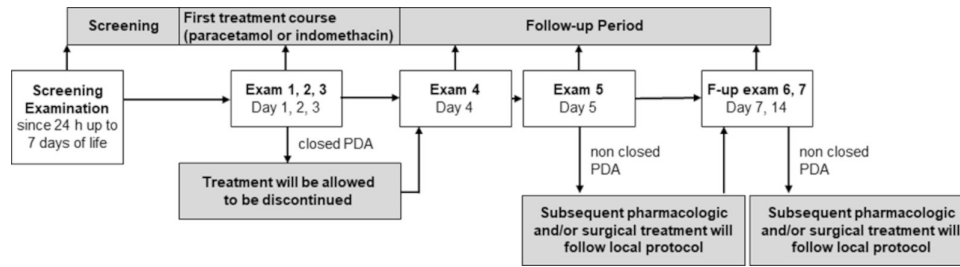


Figure 1 Study procedures flow chart. PDA, patent ductus arteriosus.

- ▶ Preterm infants with GA of 24–35 weeks and with BW of 500–2000 g.
- ▶ Infants aged 24 hours to 7 days.
- ▶ Obtaining valid informed parental consent for entry of an infant into a clinical trial.

Initial assessment

Eligible infants will be assessed between 24 hours and 7 days of life after obtaining parental consent. A cranial and cardiac ultrasound will be performed by a neonatologist. At this time point and each subsequent assessment point (days 1–5), ultrasound parameters include the diameter of DA, LA/Ao ratio, reverse diastolic flow in the superior mesenteric artery or anterior cerebral artery, and presence and grade of IVH will be classified according to Papile *et al.*¹⁸

Interventions

Each infant will be allocated to one of the following two interventions as their initial pharmacotherapy for PDA (figure 3).

Intravenous paracetamol

The decision on the paracetamol dose regimen required careful consideration because the potential for hepatotoxicity due to the accumulation of toxic metabolites, particularly in the immediate neonatal period when paracetamol clearance may be low. Dose regimens of 15 mg/kg intravenous every 6 hour for 3 days have been used in most published data investigating the treatment of PDA using intravenous paracetamol,^{19–21} this regimen will be used in this study (figure 3A).

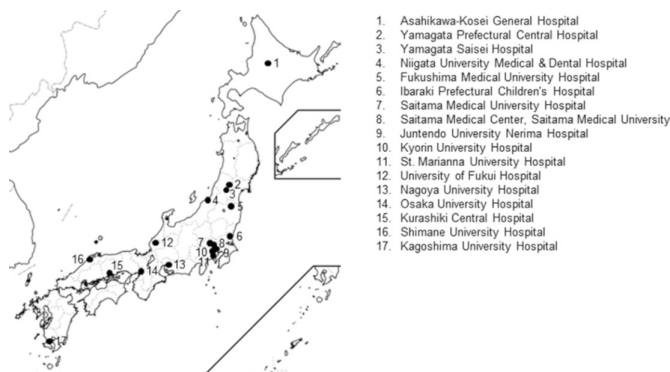


Figure 2 Study setting. The study will take place at 17 Japanese Neonatal Intensive Care Units.

Intravenous indomethacin

The indomethacin dose regimen of 0.1–0.2 mg/kg intravenous every 24 hours for 3 days will be used according to its medical package insert (figure 3B).

Allocation

Randomisation will be achieved by using randomly generated treatment allocations using web-based software. We will use the 1:1 stratified block randomisation, and the stratification will be based on GA (23–27 weeks; 28–35 weeks) and low-dose prophylactic indomethacin to prevent IVH (treatment; no treatment).

Unblinding

The open-label design is selected because¹ the different dose schedule of paracetamol and indomethacin makes the double-blind design inapplicable and² the primary outcome (renal dysfunction) is objectively detected by clinical data (serum creatinine levels and urine output) and cannot be affected by the open-label-condition. However, to minimise bias, strict criteria and definitions for hPDA will be maintained during the trial.

Routine assessments

All infants will be routinely assessed from 24 hours to 7 days of age based on the results of cranial and cardiac ultrasound. Findings will be communicated to the treatment team who will decide on the haemodynamic significance of PDA. The trial intervention will be discontinued if there is evidence of congenital heart disease (not including patent foramen ovale and left superior vena cava remnant), pulmonary hypertension diagnosed by echocardiography (presence of right-left shunt of foramen ovale or DA), and IVH (grade 3 or 4). The treatment will be allowed to be discontinued in cases where the DA is closed during a treatment course. The following routine

A. Paracetamol dose regimen

Dose (mg/kg)											
Day 1				Day 2				Day 3			
1st	2nd	3rd	4th	1st	2nd	3rd	4th	1st	2nd	3rd	4th
15	15	15	15	15	15	15	15	15	15	15	15

B. Indomethacin dose regimen

Time after birth at the first dose	Dose (mg/kg)		
	Day 1	Day 2	Day 3
<48 hours	0.2	0.1	0.1
≥2 days	0.2	0.2	0.2

Figure 3 Participant treatment regimen.



assessment will be performed on days 1, 2, 3, 4, 5, 7 and 14. Additional interim assessments may be performed as clinically indicated. At all times, infants will remain under the care of the treating neonatologist. Clinical decisions, including PDA management, will always be at the discretion of the treating team. Ongoing management of the PDA after 3 days will continue as per the treating team.

Data collection methods

The following variables will be recorded for infants included in the study: birth date, sex, GA, BW, Apgar score at 1 and 5 min, date when hsPDA is diagnosed, history of prior treatment, medical history, complications, maternal age, gravidity, parity, mode of delivery, plurality, exposure to antenatal steroids, maternal history of hypertensive disease of pregnancy or premature rupture of membranes. Clinical outcomes will be assessed until day 14.

Outcomes

Primary

1. Renal dysfunction from the start of treatment to 48 hours after the last dose of the study drug.

Secondary

- Closure of PDA 24 hours after the end of treatment.
- Successful treatment (weaning from hsPDA) 24 hours after the end of treatment.
- Reopening of PDA 24–48 hours after the end of treatment.
- Gastrointestinal bleeding from the start of treatment to 48 hours from the last dose of the study drug.
- Gastrointestinal perforation from the start of treatment to 48 hours from the last dose of the study drug.
- Side effects** from the start of treatment to 48 hours from the last dose of the study drug.
**Side effects are defined as an appreciably harmful or unpleasant reaction resulting from an intervention related to the use of a medicinal product.
- Changes in the following laboratory values from the day of the start of treatment to 24 and 48 hours from the last dose of the study drug: platelet count, BUN, serum creatinine, serum bilirubin, serum aspartate aminotransferase (AST), serum alanine aminotransferase (ALT), 24 hours urine output (mL/kg/H) and N-terminal pro-B-type natriuretic peptide (NTproBNP).

Outcome data definitions

- Renal dysfunction: (1) serum creatinine level ≥ 0.3 mg/dL or 1.5-fold increase from baseline or (2) urine output < 1 mL/kg/H (24 hours).

Rescue treatment and discontinuation of intervention

If closure of the DA is not achieved within 48 hours from the last dose of the study drug or if the DA reopens, optimal treatment considered by the physician, including intravenous acetaminophen, indomethacin and ibuprofen and surgical closure, shall be administered. The protocol treatment will be discontinued in the following cases: (1)

if the physician determines that the study drug cannot be administered due to medical reasons arising after enrolment, (2) when the urine output in the 24 hours before administration is anuria or marked oliguria (urine output: < 0.6 mL/kg/hour), no indomethacin should be administered and intravenous indomethacin therapy should be withdrawn or (3) when the ALT or AST rises more than three times the normal value (ALT 6–50 U/L; AST 35–140 U/L), no paracetamol should be administered and intravenous paracetamol therapy should be withdrawn.

Other medications

Concomitant prohibited treatment

The following concomitant medications are prohibited during protocol treatment and for 48 hours from the last dose of the study drug: (1) ibuprofen; (2) intravenous steroids (eg, hydrocortisone, dexamethasone) and (3) indomethacin for prevention of IVH. Reasons for prohibition are the following: (1) Because it is a drug for the treatment of PDA which may affect the safety and efficacy of the protocol treatment; (2) Concomitant use may increase the risk of necrotising enterocolitis and gastrointestinal perforation and (3) Because it is the same drug as the control drug, the administration of low doses of indomethacin for the prevention of IVH before the start of protocol treatment is allowed and subject to each institution's policy.

Restricted concomitant therapy

During the protocol treatment and for 48 hours from the last dose of the study drug, diuretics (eg, furosemide) are allowed only if urine output is < 1 mL/kg/H (24 hours), because of the possibility of directly affecting the primary outcome (ie, urine output).

Supportive care

Determination of administration and dosage of catecholamine (eg, dopamine, dobutamine), the volume of transfusion and enteral feedings, and red blood cell transfusion criteria should be following each institution's policy.

Statistical analysis

All tests of the effect of treatment on outcomes will be conducted on an intention-to-treat basis. That is, analyses will be based on assigned treatment rather than actual treatment. The analysis will be performed primarily on the full analysis set (FAS, the largest analysis population) and also on the per-protocol set (protocol-compliant population) as a secondary analysis.

Sample size

In the previous studies, the observed proportion of renal dysfunction by intravenous indomethacin was 25%.^{22 23} We considered a clinically meaningful reduction of 20% (risk difference) by intravenous paracetamol. With a one-sided significance level of 0.025, 49 enrolments per group would be required to achieve 0.8 statistical power

to reject the null hypothesis using a one-sided Z test. A target enrolment of 55 patients per group (110 patients in total) was set, assuming a 10% drop-out or ineligibility.

Recruitment

Since the number of patients at each centre is 6 cases/month, of which 4 cases/month are planned to be registered, the target number of cases is expected to be achieved sufficiently. If the target number of cases is not expected to be achieved within the study period, an extension of the study period will be considered in light of the registration rate.

Infant characteristics and baseline comparisons

Demographic and other baseline characteristics will be summarised by the assigned treatment group. For categorical variables (eg, sex and medical history), the frequency and percentage of each category are calculated for each group. For continuous variables (eg, age, GA, BW), summary statistics (mean, SD, minimum, first quartile, median, third quartile, maximum) are calculated for each group.

Analysis of the primary outcome

Renal dysfunction from the start of treatment to 48 hours from the last dose of the study drug

In analysing the primary outcome using the FAS, all participants who have missing data on renal dysfunction will be treated as 'having renal dysfunction' regardless of the reason. To confirm the hypothesis that 'the proportion of renal dysfunction in the paracetamol group is lower than in the indomethacin group', we set the null hypothesis as 'the proportion of renal dysfunction is equal between the two groups'. The p value will be calculated using a one-sided Z test of the difference in proportion. The significance level is set at 0.025, one sided. If the p value of this analysis is less than the significance level, we conclude that 'the proportion of renal dysfunction in the paracetamol group is lower than in the indomethacin group'. This analysis will be regarded as the primary analysis of this study. The proportion of renal dysfunction and its two-sided 95% CI will be also calculated for each group. In addition, the risk difference, the relative risk and their two-sided 95% CIs will be calculated.

Analysis of secondary outcomes

(1) closure of PDA, (2) successful treatment, (3) reopening of PDA, (4) gastrointestinal bleeding, (5) gastrointestinal perforation and (6) side effects

For secondary outcomes 1–6, the proportion of each outcome and its two-sided 95% CI will be calculated for each group. In addition, the risk difference, the relative risk and their two-sided 95% CIs will be also calculated.

(7) Changes in the laboratory values (platelet count, BUN, serum creatinine, serum bilirubin, AST, ALT, urine output, NTproBNP)

For secondary outcome (7), summary statistics for each group will be calculated at the start date of study drug administration, 24 and 48 hours from the last dose of

the study drug, and a box plot will be also created. The mean and the change from baseline in each time point and these two-sided 95% CIs will be also calculated. In addition, the mean difference between groups and their two-sided 95% CIs will be calculated.

Interim analysis

An interim analysis will not be performed in this study.

Patient and public involvement in study design

No patient was involved.

ETHICS AND DISSEMINATION

Ethics

This trial is a clinical study to evaluate the safety and efficacy of a drug that is approved for the treatment of pain and fever in children but is not indicated for the treatment of PDA in premature infants. Therefore, this trial will be conducted in compliance with the law on clinical research. Furthermore, the trial will be conducted following the World Medical Association Declaration of Helsinki.

Consent

Parent of eligible infants are informed of the purpose of the study, what is involved, the possible risks of study participation, the voluntary nature of participation, the right to withdraw and protection of confidentiality by the investigators. The parent is provided with a written information sheet, and evidence of informed consent is obtained in writing.

Safety Monitoring

Liver function tests will be used to monitor infants for evidence of hepatotoxicity during the treatment period if needed and at 24 and 48 hours from the last dose of the study drug. Blood paracetamol levels will also be checked 24 hours after the last dose of the study drug to investigate the pharmacokinetics of paracetamol in this population. These results of paracetamol concentration will not be made available to clinical staff or study personnel.

Trial discontinuation

Whether or not to continue the trial will be considered in consultation with the advisory committee for the safety and efficacy assessment in the following cases: (1) when significant information regarding the quality, safety or efficacy of the study drug is obtained; (2) when there is a recommendation for discontinuation by the regulatory authority; (3) when there is a recommendation or instruction for discontinuation by the clinical research review committee at the site and (4) other circumstances necessitating discontinuation or suspension of the research.

Data and safety monitoring board

The monitoring work at each institution will be outsourced to the National Center for Child Health and Development

as a data monitoring committee. Central and site monitoring will be conducted to ensure that subjects' human rights are protected, that the research is conducted safely and in compliance with the research protocol and that data are collected accurately. Central monitoring will be conducted on the electronic case report form data collected at Electronic Data Capture. Site monitoring will be conducted at the institution and will cover the implementation system of the trial, the implementation procedures, and the preparation and preservation of records.

Data management

The study will be conducted under applicable Privacy Acts and Regulations. Personal information must not be obtained by fraud or coercion. Personal information collected in the trial will be handled within the scope of consent obtained from the parent. Anonymisation of medical data and consent forms will be achieved by assigning a subject identification code and creating a correspondence table. The corresponding table will be kept in a locked archive under strict control. All study-related documentation will be maintained for 5 years following the discontinuation or completion of the trial.

Auditing

No audits will be conducted in this study.

Dissemination policy

The results of the trial are expected to be published in a scientific journal and presented at medical conferences. The final reporting will follow the Consolidated Standards of Reporting Trials Report guidelines (<http://www.consort-statement.org>).

Informed consent materials

The participant consent form is provided as online supplemental file 2.

Biological specimens

The remaining blood used for haematological tests and serum used for biochemical tests and blood concentration measurement will be discarded by the principal investigator following the policies of each storage facility or laboratory.

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Contributors FN conceived and designed the study under the supervision of KaK, MS, MM and KU. FN, MH, SS, YM and KO contributed to reviewing the existing literature. KoK and NF are responsible for pharmacokinetic analysis. FN drafted the manuscript. All authors (FN, MH, SS, YM, KaK, MS, KO, MM, KoK, NF and KU) reviewed and revised the manuscript, providing important intellectual content and approved the final version.

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