



# Safety and Feasibility of Intravenous Paracetamol for Patent Ductus Arteriosus in Indomethacin-/Ibuprofen-Resistant or -Contraindicated Preterm Infants: A Case Series

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## Abstract

**Background** Although indomethacin and ibuprofen are the standard treatments for hemodynamically significant patent ductus arteriosus (hsPDA), they are associated with renal impairment and gastrointestinal complications. Paracetamol for hsPDA closure does not provoke a peripheral vasoconstrictive effect and seems to have effects similar to those of indomethacin and ibuprofen. We have previously reported the safety of low-dose (7.5 mg/kg) intravenous paracetamol for preterm infants with hsPDA, who were indomethacin-resistant or -contraindicated but did not affect the need for surgical PDA ligation. However, reports considering the use of higher-dose (15 mg/kg) paracetamol for hsPDA have not been published in Japan.

**Cases** In 16 premature infants in whom indomethacin or ibuprofen was contraindicated or ineffective, 15 mg/kg of paracetamol was intravenously administered every 6 hours for 3 days after obtaining parental consent. hsPDA closure or narrowing was observed in 14 infants (88%), with the need for surgical closure totally avoided in nine cases (56%). High plasma paracetamol levels were observed in three cases. No paracetamol-related side effects or adverse events were reported.

**Conclusion** The intravenous administration of higher dose paracetamol was safe and feasible in premature infants with hsPDA. Future clinical trials to explore the optimized dose and timing of administration are needed.

## Keywords

- ▶ ibuprofen
- ▶ indomethacin
- ▶ paracetamol
- ▶ patent ductus arteriosus
- ▶ premature infant
- ▶ surgical closure

## Background

Ductus arteriosus (DA) is an essential blood vessel for fetal circulation and development. In most term infants, DA closes spontaneously within 1 to 2 days after birth due to the loss of the prostaglandin supply from the placenta and the rise of

arterial oxygen pressure.<sup>1</sup> In contrast, DA often does not close spontaneously in preterm infants, including especially very-low-birth-weight infants (VLBWIs), due to the poor responsiveness to arterial oxygen pressure and the high responsiveness to prostaglandin inherent in this population.<sup>2,3</sup> It is well known that hemodynamically significant

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patent ductus arteriosus (hsPDA) increases the risk of intraventricular hemorrhage (IVH), necrotizing enterocolitis, and bronchopulmonary dysplasia.<sup>4–6</sup> In Japan, the cyclooxygenase inhibitor—indomethacin—has been used as standard therapy for hsPDA. In addition, another cyclooxygenase inhibitor—ibuprofen—has been available for application in cases of hsPDA since June 2018. However, because of their side effects such as acute kidney injury and gastrointestinal perforation, the introduction of other novel treatments for hsPDA with fewer side effects is required.<sup>6</sup>

Paracetamol has recently been reported to have the same effects on DA closure with fewer side effects as those of indomethacin and ibuprofen observed during the treatment for hsPDA.<sup>7–12</sup> We have previously reported a case series of three patients in Japan treated with low-dose intravenous paracetamol (7.5 mg/kg, given every 6 hours for 3 days) for preterm infants with hsPDA, who were indomethacin-resistant or -contraindicated. A temporary DA closure was observed in two of the three infants without any side effects. However, all three infants eventually required surgical closure.<sup>13</sup> This treatment failure was thought to be due to an inadequate dose of paracetamol, given that a higher dose (15 mg/kg, given every 6 hours for 3 days) has been used in most studies, elsewhere in which degree of the efficacy of paracetamol on DA closure was observed.<sup>7–11</sup> Therefore, in the present research, we increased the dose of paracetamol up to 15 mg/kg/dose for evaluation in 16 preterm infants who were indomethacin/ibuprofen-resistant or -contraindicated and examined the safety and feasibility outcomes.

## Methods

About 16 VLBWIs (birth weight <1,500 g) with hsPDA born at Saitama Medical Center, Saitama Medical University from July 1, 2017 to March 31, 2019 were included in this research. hsPDA was determined by each physician using echocardiography and ultrasonography of the brain and abdomen. These patients showed resistance or contraindications, such as acute renal failure, to indomethacin and/or ibuprofen. In each patient, 15 mg/kg/dose of paracetamol (Acelio Intravenous Injection; TERUMO Co. Ltd., Tokyo, Japan) was administered every 6 hours for 3 days as one course. Arterial duct diameter, left atrial aortic root ratio, and end-diastolic flow velocity of the left pulmonary artery were subsequently evaluated using ultrasonography by the physician. Physical examinations; vital signs; and blood tests including creatinine (Cr), aspartate aminotransferase (AST), alanine aminotransferase (ALT), and acetaminophen blood levels were performed to evaluate the presence of adverse events. Acute renal failure was defined as serum Cr level >1.5 mg/dL. Elevated AST and ALT levels were defined as >100 and >280 U/L, respectively. This study was covered by the clinical trial insurance program, and was approved by the institutional review board of Saitama Medical Center, Saitama Medical University (approval no. 1656-III). Parental consent was obtained before paracetamol administration.

## Results

About 16 patients were included in this study (► **Table 1**). The median gestational age was 27.6 weeks (range: 23.0–29.4 weeks) and the median birth weight was 913 g (range: 475–1,423 g). Paracetamol was administered because of resistance to indomethacin or ibuprofen in seven cases and the presence of acute kidney injury in ten cases (one case had both findings). The median starting date of paracetamol administration was a day 10 after birth (range: days 2–36), and the median duration of paracetamol administration was 6 days (range: 3–9 days). The initial median DA diameter was 1.3 mm (range: 0.8–2.2 mm), and the initial median left atrial aortic root ratio was 1.66 (range: 0.87–2.08). Among the 16 cases, paracetamol treatment was effective in 14 cases (88%), with DA closure or narrowing observed, while two cases (13%) were refractory to the therapy. Surgical closure of PDA was required in seven cases (44%), and the DA remained open at discharge and was followed up on an outpatient basis in one case (6%).

In all 16 cases, no adverse events—including elevated AST or ALT levels, hypothermia (<36°C body temperature), or the need for a higher incubator temperature—were observed after paracetamol administration. Plasma paracetamol levels were measured in ten cases (► **Fig. 1**). In two (cases 7 and 13) of the ten cases, the third course of paracetamol administration was avoided because relatively high plasma paracetamol levels (64.3 and 97.7 µg/mL, respectively) were observed at 6 hours after the earlier two courses of paracetamol treatments. In addition, in one case (case 16), plasma paracetamol level of 116.7 µg/mL was observed 4 hours after the first course of treatment, so the second course was discontinued.

In case 1, colostomy was performed on day 5 after the birth for congenital intestinal atresia, and ascites could not be controlled thereafter, resulting in death on day 64. Cases 2 and 3 were monozygotic diamniotic twins with twin-to-twin transfusion syndrome, and both patients had periventricular leukomalacia from birth. Case 14 developed IVH on day 1 after birth with circulatory failure due to intrauterine infection. Case 16 was born with fetal heart failure and fetal hydrops, and had IVH and intracerebral hemorrhage.

## Discussion

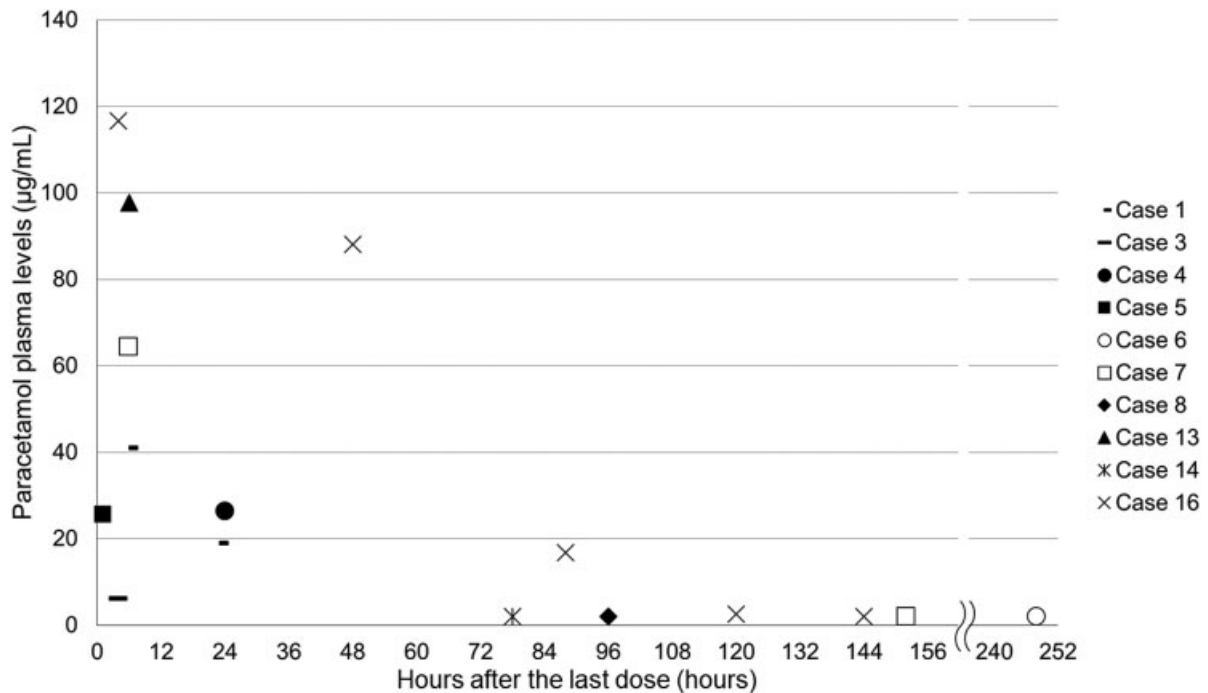
In this case series, we confirmed the safety and feasibility of higher-dose intravenous paracetamol (15 mg/kg given every 6 hours for 3 days) for VLBWIs with hsPDA who were indomethacin/ibuprofen-resistant or -contraindicated in Japan, similar to that previously observed in patients with low-dose intravenous paracetamol (7.5 mg/kg, given every 6 hours for 3 days).<sup>13</sup>

In our previous study performed using low-dose intravenous paracetamol (7.5 mg/kg given every 6 hours for 3 days), temporary DA closure was observed in two of three (67%) cases with hsPDA and no short-term adverse events occurred during the provision of pharmacological treatment in any cases. However, our protocol of applying low-dose intravenous paracetamol ultimately could not avoid the need for surgical

**Table 1** Summary of cases

Case	GA (wk)	BW (g)	Contraindication to indomethacin/ibuprofen	Age when treatment was started (d)	Duration of treatment (d)	Pretreatment DA diameter (mm)	Pretreatment LA/Ao	Posttreatment PDA status	Adverse events	Surgical ligation	PDA status at discharge
1	24	653	Ineffective + acute renal failure	4	6	1.6	1.77	Temporary closure	-	+	Closed
2	28	1,053	Acute renal failure	2	3	1.3	1.96	Closed	-	-	Closed
3	28	721	Acute renal failure	3	3	2	1.68	Closed	-	-	Closed
4	25	1,036	Acute renal failure	20	3	1	1.59	Ineffective	-	+	Closed
5	29	1,363	Ineffective	24	3	1.5	1.73	Temporary closure	-	-	Closed
6	29	1,173	Ineffective	25	6	2.1	2.08	Narrowing	-	-	Open
7	26	920	Ineffective	5	6	1.2	1.48	Narrowing	-	+	Closed
8	23	475	Acute renal failure	9	6	1.0	1.24	Narrowing	-	+	Closed
9	28	905	Acute renal failure	6	6	1.2	1.63	Closed	-	-	Closed
10	23	517	Acute renal failure	8	9	1.1	1.32	Closed	-	-	Closed
11	28	820	Ineffective	14	9	1.1	1.88	Temporary closure	-	-	Closed
12	24	695	Acute renal failure	36	3	0.8	0.87	Closed	-	-	Closed
13	23	565	Acute renal failure	6	3	1.2	1.52	Temporary closure	-	-	Closed
14	27	1,015	Ineffective	11	9	2	1.70	Narrowing	-	+	Closed
15	28	1,083	Ineffective	25	3	2.2	1.29	Narrowing	-	+	Closed
16	28	1,423	Acute renal failure	3	9	1.9	2.03	Ineffective	-	+	Closed

Abbreviations: BW, birth weight; DA, ductus arteriosus; GA, gestational age; LA/Ao, left atrial/aortic root ratio; PDA, patent ductus arteriosus.



**Fig. 1** Plasma paracetamol levels. The plasma paracetamol levels were measured in ten cases. The x-axis shows hours after the last dose of paracetamol (hours) and the y-axis shows plasma paracetamol levels ( $\mu\text{g/mL}$ ).

treatment (avoidance rate of surgical ligation: 0%). In contrast, the presently discussed pharmacological treatment approach with higher-dose intravenous paracetamol (15 mg/kg given every 6 hours for 3 days) increased both the success of DA closure or narrowing (14/16; 88%) and avoidance of surgical PDA ligation (9/16; 56%) as compared with the low-dose paracetamol regimen. In a systematic review, the analysis of uncontrolled studies suggested that as compared with the use of low-dose paracetamol (30–60 mg/kg/day), the use of higher doses (60 mg/kg/day) appears unnecessary because of no significant differences in DA closure rate between two doses.<sup>10</sup> However, this result should be interpreted with caution considering the high proportion of subjects with a gestational age of more than 28 weeks treated with low doses. Therefore, higher-dose (15 mg/kg/dose) paracetamol should be used in further clinical trials involving patients with PDA who have resistance or contraindications to indomethacin and/or ibuprofen.

Of note, paracetamol clearance is lower in neonates than in children and adults. After metabolic conversion, conjugation with glucuronic acid and sulfate, paracetamol is subsequently eliminated via the renal route. In the present study, the plasma paracetamol levels were measured in ten cases. With acute ingestions of paracetamol, the Rumack-Matthews nomogram is a valuable tool to use to assess the risk of hepatotoxicity. This nomogram was originally constructed in the 1970s as a method to discriminate those patients who were more likely to suffer hepatotoxicity and those who were not. A line between 200 mg/mL at 4 hours after ingestion and 25 mg/mL at 16 hours, known as the “200 line” defined the group at risk.<sup>14</sup> Conversely, a parallel line at 150 mg/mL at 4 hours—also known as the treatment line or “150 line”—is

the treatment line most commonly used in the United States.<sup>15</sup> Although no paracetamol-related adverse events—including elevated AST or ALT levels—were observed in any patients in this research, another course of paracetamol administration was avoided because of high plasma paracetamol levels in three of ten cases in which plasma paracetamol levels were measured. All three cases had circulatory failure, oliguria, or elevated serum Cr levels before and during intravenous paracetamol treatment. Therefore, we stress that plasma paracetamol levels should be monitored in patients who are at a high risk for circulatory and/or renal failure.

We determine that good feasibility and short-term safety were present during pharmacological treatment with intravenous paracetamol in our research. However, it has been reported that the long-term administration of paracetamol to the pregnant mother is implicated in the development of autism or autism spectrum disorder in children.<sup>16</sup> In contrast, however, one study reported that there were no differences in neurodevelopmental outcomes at 18 to 24 months, including on the Bayley Scales of Infant Development, second edition; the Mental Developmental Index; and the Psychomotor Developmental Index, with recommended adaptations suggested for visual and auditory impairments in preterm or low-birth weight infants exposed to paracetamol as compared with ibuprofen for PDA.<sup>17</sup> Importantly, because the quality of evidence of this study is low, long-term follow-up to at least 18 to 24 months after birth must be incorporated in any studies of paracetamol in the newborn population, including our previous and present case series.

In our current case series, several limitations exist. (1) Being a descriptive study with a small number of patients

and with the absence of a control group weakens our study, especially in the presence of several published randomized controlled pilot studies suggesting the efficacy and safety of paracetamol for hsPDA.<sup>8–11</sup> However, those studies also included a limited number of cases. Therefore, reporting a case series still has some degree of enhancement to the quality of evidence as part of a cumulative data. (2) We confirmed the treatment's safety and feasibility with the anticipated results and a lack of serious adverse reactions in small populations whose treatment with paracetamol were determined by physician's discretion. To estimate the efficacy of this treatment in hsPDA patients, randomized control trials are warranted in the future.

## Conclusion

This is the first report in Japan describing the safety and feasibility of treatment with higher dose intravenous paracetamol for preterm infants with hsPDA in whom indomethacin or ibuprofen was contraindicated or ineffective. Plasma paracetamol levels should be monitored in higher risk patients with circulatory and/or renal failure. Further follow-up study among these subjects and the conduction of prospective clinical trials such as randomized control trials are needed to evaluate the long-term prognosis and efficacy of intravenous paracetamol for hsPDA closure.

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### Conflict of Interest

None declared.

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