



Combination Therapy with Acetaminophen and Ibuprofen for Patent Ductus Arteriosus in Extremely Preterm Infants: A Retrospective Study in South Korea

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Objective: This study aimed to investigate the closure rate and adverse effects of combination therapy with acetaminophen and ibuprofen for hemodynamically significant patent ductus arteriosus (hsPDA) compared with monotherapy with ibuprofen in extremely preterm infants (EPTs).

Methods: This was a single-center, retrospective, and historical control study of infants with hsPDA born at <28 weeks of gestation and a birth weight <1,000 g. Based on the first-line therapeutic policy for hsPDA, the cohort was classified into a monotherapy group (period I: January 2019-July 2021) and a combination therapy group (period II: September 2021-August 2023). Baseline characteristics, treatment outcomes, adverse effects, and morbidities were compared between the groups.

Results: Of the 43 EPTs with hsPDA, 26 received monotherapy with ibuprofen during period I, and 17 received combination therapy with acetaminophen and ibuprofen during period II. The successful closure rates after the first medical therapy were 42.3% in the monotherapy group vs. 76.5% in the combination therapy group ($P=0.027$). No significant difference in adverse effects during medication use was observed between the groups.

Conclusion: Combination therapy with acetaminophen and ibuprofen improved the closure rate for hsPDA without detectable adverse effects. Combination therapy could be considered the first therapeutic option for hsPDA in EPTs. Further well-designed studies are needed to define the safety and effectiveness of combination therapy.

Key Words: Acetaminophen, Patent ductus arteriosus, Ibuprofen, Newborn

Introduction

The ductus arteriosus (DA) is a fetal structure that plays a crucial role in blood circulation.¹ In term infants, the DA typically closes within the first few days to weeks of life. In extremely preterm infants (EPTs) (born at <28 weeks of gestation), the DA often fails to close due to the immaturity of the signaling pathways involved in its closure.² Approximately 60% to 80% of EPTs persist in having a patent DA (PDA).^{3,4} Persistent PDA in EPTs, leading to left-to-right shunts, which may increase the risk of adverse outcomes, including prolonged ventilator support, bronchopulmonary dysplasia (BPD), pulmonary hemorrhage, necrotizing enterocolitis (NEC), and intraventricular hemorrhage (IVH).^{1,5,6} When a PDA is associated with clinical and echocardiographic signs of pulmonary over-circulation and systemic hypoperfusion, this is defined as a hemodynamically significant

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PDA (hsPDA).⁶ Although there is limited consensus on the optimal diagnostic approach for hsPDA, clinical suspicion should be confirmed with echocardiography (ECHO) with color Doppler before considering treatment.^{7,8}

The management of hsPDA is one of the most controversial topics in the care of preterm infants. Despite abundant clinical research and experience, the optimal timing and approach for hsPDA treatment in EPTs, in whom the ductus is resistant to pharmacological treatment, has not yet been established.^{2,6} Conservative management includes targeted ventilation strategies, fluid restriction, and diuretic therapy to counteract the effects of the PDA shunt.² Currently, the most preferred first-line therapeutic approach to hsPDA is pharmacotherapy using ibuprofen.^{8,9} Ibuprofen non-selectively inhibits cyclooxygenase enzymes and prevents the conversion of arachidonic acid to prostaglandins (PG), which plays a central role in maintaining ductal patency. Over the last decade, acetaminophen (paracetamol), which prevents the conversion of arachidonic acid to PGE2 by inhibiting the peroxidase segment of PG synthase, has emerged as a potential therapeutic option for hsPDA.¹⁰ To date, with the action of the 2 separate pathways that inhibit PG production, combination therapy with ibuprofen and acetaminophen has been proposed as a novel strategy for hsPDA. Results from a small number of randomized controlled trials and observational studies have provided early evidence of possible improved efficacy of combination therapy with ibuprofen and acetaminophen for hsPDA in preterm infants without any increased adverse effects.¹¹⁻¹⁴

Based on the available data, we adopted combination therapy with acetaminophen and ibuprofen as the first-line therapy for hsPDA after September 2021. This study aimed to investigate whether combination therapy for hsPDA is associated with an improved successful closure rate. We also evaluated the side effects and adverse outcomes of combination therapy using acetaminophen and ibuprofen in most preterm infants.

Methods

1. Study population

We included all infants with a diagnosis of hsPDA who were

born at <28 weeks of gestation and birth weight <1,000 g and were admitted to Gachon University Gil Medical Center neonatal intensive care unit between January 2019 and August 2023. Infants who died or had major congenital anomalies, IVH $\geq$ grade 3, persistent pulmonary hypertension, or any significant genetic conditions prior to diagnosis of hsPDA were excluded. hsPDA was diagnosed based on ECHO findings of a left-to-right shunt and/or clinical signs. If the PDA closed spontaneously or did not require any treatment due to the absence of PDA-related signs or symptoms, it was defined as non-hsPDA. During the study periods, 2 distinct therapeutic policies were implemented for the management of hsPDA with no changes in the basic treatment protocol for fluid therapy and enteral feeding. Based on the therapeutic policy, we classified the infants into 2 cohort groups: a combination therapy group (period II: September 2021–August 2023) and a monotherapy group as historical controls (period I: January 2019–August 2021).

2. Therapeutic protocol of infants with hsPDA according to study periods

In period I, ibuprofen monotherapy was the first-line therapeutic choice for hsPDA in EPTs. Medical treatment was initiated at least 48 hours after birth to avoid unnecessary drug exposure. During the first week of life, we administered ibuprofen (at the initial dose of 20 mg/kg per rectum) after diagnosis by ECHO, even though no clinical signs of hemodynamic instability. However, after a week of life, treatment was initiated only for those who have echocardiographic findings and clinical symptoms/signs of hsPDA. ECHO was repeated every 24 hours to decide on additional administration of ibuprofen up to 3 times if it did not meet the criteria for successful DA closure. If the echocardiographic findings and clinical conditions improved, the additional administration of ibuprofen was discontinued. The second medical therapy was performed with the second cycle of ibuprofen (20 mg/kg/dose every 24 hours for a total of 3 doses per rectum) or a cycle of acetaminophen (15 mg/kg/dose every 6 hours for a total of 12 doses, intravenous) in infants who showed a slight but not significant improvement in ECHO findings and clinical conditions within 48 hours of completion of the first treatment course. Surgical ligation was performed if hsPDA

failed to close after a second medical therapy or if ibuprofen treatment was contraindicated.

In period II, infants with hsPDA received combination therapy with acetaminophen and ibuprofen concurrently as first-line medical therapy. Ibuprofen was discontinued if DA closure was confirmed by ECHO, in the same way as described for period I. Surgical ligation was performed if the PDA failed to close after the first cycle of combination pharmacotherapy.

3. Diagnosis of hsPDA

ECHO was performed by a neonatologist (DWS) to confirm the normality of the cardiac anatomy and exclude congenital heart diseases. The presence of hsPDA was confirmed using ECHO within a week of birth. Echocardiographic criteria for diagnosing hsPDA were listed in order of significance as follows: left-to-right shunting of blood through the DA and (1) end-diastolic flow velocity of the left pulmonary artery (DFLPA) to systolic flow of the left pulmonary artery (SFLPA) ratio: >0.3 ; (2) DFLPA >0.3 m/s; (3) fluctuation of perfusion waveform in the internal cerebral vein;¹⁵ (4) left atrium-to-aortic root (LA: Ao) ratio >1.6 ; (5) no restrictive pattern of ductal flow (no mosaic); or (6) end-diastolic reversal of blood flow in the superior mesenteric artery or the anterior cerebral artery.

Clinical symptoms and signs suggestive of hsPDA were defined as the presence of the following: (1) pulsations of the precordium, (2) systolic murmur, (3) tachycardia (heart rate >160 bpm), (4) apnea or mechanical ventilation, (5) bounding femoral pulse, (6) hepatomegaly, (7) metabolic acidosis, and (8) respiratory deterioration.¹⁶

The diagnosis of hsPDA was made based on at least 3 of the above echocardiographic indices and/or the presence of clinical symptoms and signs. Successful closure was defined as a case in which the DA was closed or the restrictive pattern of blood flow in the DA, DFLPA/SFLPA <0.1 , improvement in symptoms, and no need for additional therapy (either medical or surgical) for the PDA throughout the remainder of the neonatal intensive care unit stay.

4. Data collection

Clinical characteristics, including gestational age, birth weight, sex, multiple gestation, mode of delivery, antenatal

steroid treatment, rupture of membrane, maternal diabetes mellitus, chorioamnionitis, Apgar score at 1 minute and 5 minutes, surfactant administration, mechanical ventilation at treatment onset, FIO₂ at the time of treatment, and postnatal age in days at treatment, were collected from all patients. The closure rate after the first medical therapy, the closure after the second medical therapy, or surgical ligation were analyzed between the groups. To assess the adverse effects, we analyzed complete blood count, alanine aminotransferase level, serum creatinine level, spontaneous bowel perforation, and urine output between the initiation of therapy and a week after the last dose of the first medical therapy. Oliguria was defined as a urine output of <1.0 mL/kg/d for 24 hours. Adverse outcome measures included the duration of invasive ventilation and hospital stay, BPD $\geq$ moderate,¹⁷ IVH $\geq$ grade 3,¹⁸ retinopathy of prematurity (ROP) $\geq$ stage 2,¹⁹ NEC $\geq$ Bell stage 2b,²⁰ and mortality during hospitalization.

5. Statistical analysis

Statistical analyses were performed using IBM SPSS ver. 26.0 (IBM Corp., Armonk, NY, USA). The clinical characteristics of each group were described using mean $\pm$ standard deviations, median (interquartile ranges, IQR), or numbers (%). Statistical differences between the study periods were calculated using the chi-square test or Fisher's exact test for categorical variables and the Student t-test for numerical variables. Cumulative distribution function plots were analyzed between the groups to demonstrate the probability of hsPDA closure according to the differences in management. Statistical significance was set at $P < 0.05$.

6. Ethics approval

This single-center, retrospective, and historical control study was approved by the Institutional Review Board of Gachon University Gil Medical Center (GAIRB2023-106) and patients' consents were waived.

Results

During the study period, of the 78 EPTs with a birth weight $<1,000$ g, 17 infants were excluded because 15 infants died,

one infant had IVH grade 4, and one infant had persistent pulmonary hypertension before a diagnosis of hsPDA. Of the remaining 61 infants, 11 of 37 (29.7%) infants and 7 of 24 (29.2%) infants had non-hsPDA during periods I and II, respectively ($P=0.962$). Finally, analysis was performed for 26 and 17 infants enrolled in the monotherapy group and combination therapy group, respectively (Fig. 1). The baseline clinical characteristics of the patients in the study groups are summarized in Table 1. The median gestational age and mean birth weight were similar between the groups (25.7 weeks [IQR, 24.6–27.1], 748 ± 159 g in the monotherapy group vs. 25.2 weeks [IQR, 23.8–26.8], 702 ± 148 g in the combination therapy group, $P=0.464$, $P=0.343$, respectively). The median postnatal age at first treatment was 4 days (IQR, 3–6) and 3 days (IQR, 2–5) in the monotherapy group and combination therapy group, respectively ($P=0.525$). There was no significant difference in the number of ibuprofen administration in the first medical therapy between the groups. The other variables did not differ significantly between the groups.

Successful DA closure after the first medical therapy was significantly different between the groups (11/26 [42.3%] in the monotherapy group vs. 13/17 [76.5%] in the combination therapy group, $P=0.027$). In the monotherapy group, 11 infants received a second medical therapy, with one receiving a second cycle of ibuprofen and 10 receiving acetaminophen. Among those who received acetaminophen as a second medical therapy, treatment success was observed in 4 infants. Finally, 11 of 26 (42.3%) infants were treated with surgical

ligation in the monotherapy group, whereas only 4 of 17 (23.5%) infants required ligation in the combination therapy group (Table 2). The probability of hsPDA closure was higher in the combination therapy group than in the monotherapy group (Fig. 2).

No significant differences in changes in the level of creat-

Table 1. Clinical Characteristics of Study Patients

Characteristic	Monotherapy (period I, n=26)	Combination therapy (period II, n=17)	P-value
Gestational age (wk)	25.7 (24.6–27.1)	25.2 (23.8–26.3)	0.464
Birth weight (g)	748±159	702±148	0.343
Male	12 (46.2)	9 (52.9)	0.663
Multiple gestation	10 (38.5)	6 (35.3)	0.834
Cesarean section	22 (84.6)	10 (58.8)	0.080
Antenatal steroids	14 (53.8)	13 (76.5)	0.133
Rupture of membrane	7 (26.9)	6 (35.3)	0.559
Chorioamnionitis,	8 (30.8)	6 (35.3)	0.757
Pregnancy-induced hypertension	5 (19.2)	1 (5.9)	0.376
Maternal diabetes mellitus	4 (15.4)	5 (29.4)	0.445
Apgar score (1 min)	5.0 (3.0–7.0)	5.0 (3.5–7.0)	0.759
Apgar score (5 min)	8.0 (7.0–9.0)	8.0 (8.0–9.0)	0.145
Surfactant treatment	26 (100.0)	17 (100.0)	
Invasive ventilation at diagnosis	25 (96.2)	17 (100.0)	1.000
FiO ₂ at first treatment	27±7	29±9	0.553
Postnatal age at first treatment (day)	4 (3–6)	3 (2–5)	0.525
No. of ibuprofen administrations			0.552
1 Dose	5 (19.2)	3 (17.6)	
2 Doses	9 (34.6)	4 (23.5)	
3 Doses	12 (46.2)	10 (58.8)	

Values are presented as median (interquartile range), mean±standard deviation, or number (%).
FiO₂, fraction of inspired oxygen.

Table 2. Outcome of Hemodynamically Significant Patent Ductus Arteriosus

Variable	Monotherapy (period I, n=26)	Combination therapy (period II, n=17)	P-value
Closure after first medical therapy	11 (42.3)	13 (76.5)	0.027
Closure after second medical therapy	4 (15.4)	0 (0)	NA
Surgical ligation	11 (42.3)	4 (23.5)	0.327

Values are presented as number (%).
NA, not applicable.

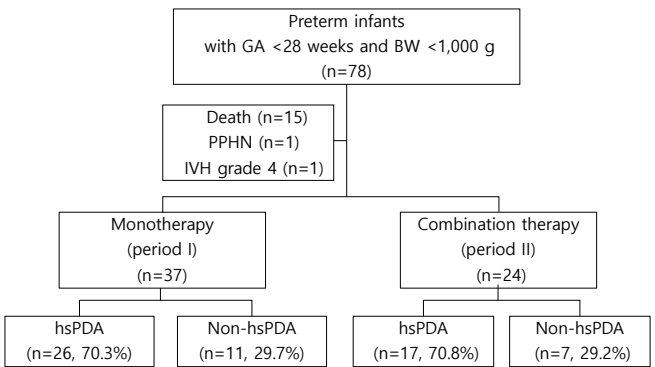


Fig. 1. Flowchart of infants included in this study. GA, gestational age; BW, birth weight; PPHN, persistent pulmonary hypertension; IVH, intraventricular hemorrhage; hsPDA, hemodynamically significant patent ductus arteriosus.

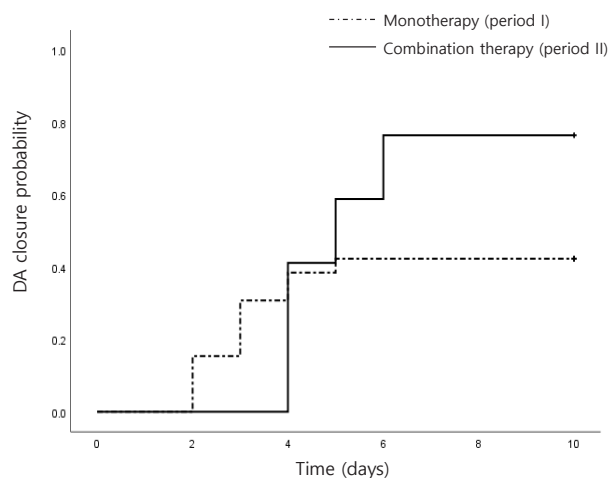


Fig. 2. Comparison of cumulative distribution function plots of ductus arteriosus closure according to differences in management between 2 groups. Combination therapy with acetaminophen and ibuprofen demonstrated a significantly higher closure probability compared with that of monotherapy with ibuprofen. DA, ductus arteriosus.

inine ($P=0.202$), ALT ($P=0.286$), platelet count ($P=0.539$), or urine output ($P=0.273$) from pre- to post-treatment were observed between the groups (Fig. 3). There were no hematologic abnormalities or hepatic impairments in the combination therapy group. None of the patients developed oliguria or spontaneous bowel perforation related to treatment in both groups. The duration of invasive mechanical ventilation and hospital stay, the incidence of BPD, IVH, ROP, NEC, and mortality during hospitalization were not significantly different between the groups (Table 3).

Discussion

This retrospective study of EPTs with hsPDA demonstrated that combination therapy with acetaminophen and ibuprofen

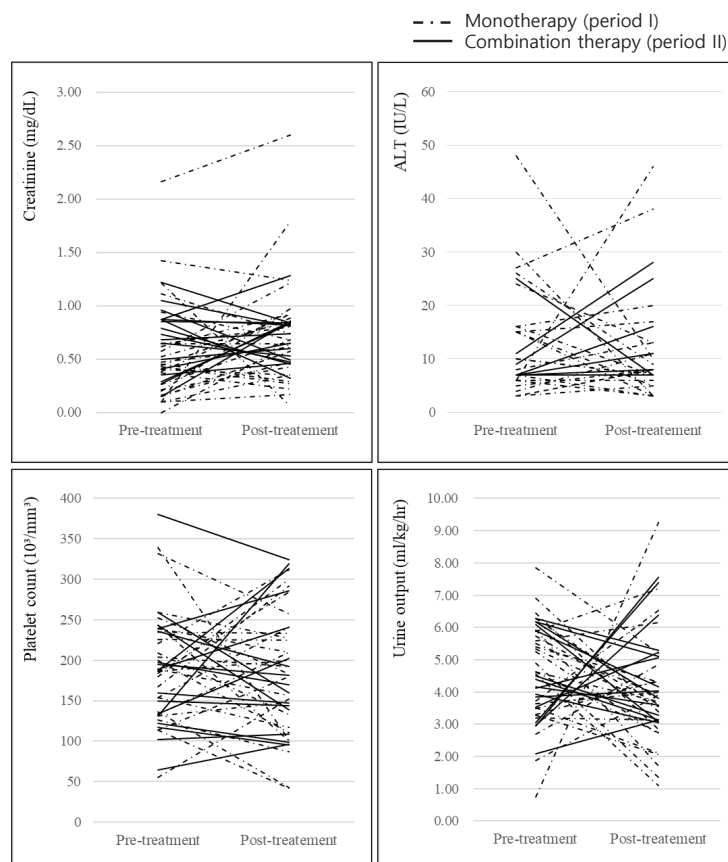


Fig. 3. Comparison of laboratory changes from pre-treatment to post-treatment between 2 groups. No significant difference was observed between the 2 groups. (A) Creatinine ($P=0.202$), (B) alanine aminotransferase ($P=0.286$), (C) platelet count ($P=0.539$), and (D) urine output ($P=0.273$). ALT, alanine aminotransferase.

Table 3. Adverse Outcome of Study Patients

Variable	Monotherapy (period I, n=26)	Combination therapy (period II, n=17)	P-value
Duration of invasive mechanical ventilation (day)	48.5±38.1	34.4±19.4	0.166
Hospital days	111.7±56.3	92.4±36.1	0.218
Bronchopulmonary dysplasia (≥moderate)	15 (57.7)	10 (58.8)	0.923
Intraventricular hemorrhage (≥grade 3)	3 (11.5)	1 (5.9)	0.642
Retinopathy of prematurity (≥stage 2)	8 (30.8)	10 (58.8)	0.096
Necrotizing enterocolitis (≥stage 2)	5 (19.2)	0 (0)	0.139
Mortality during hospitalization	5 (19.2)	2 (11.8)	0.685

Values are presented as mean±standard deviation or number (%).

may improve the closure rate of hsPDA, as compared with those of ibuprofen monotherapy. Surgical ligation was more prevalent in the monotherapy group. We found that no adverse events that were definitively attributable to combination therapy were detected. These findings suggest that combination therapy with acetaminophen and ibuprofen may be a possible first treatment option for the closure of PDA, even in EPTs.

The search for an optimal management approach for PDA in premature infants is ongoing. The failure rate for monotherapy with ibuprofen or acetaminophen for the first treatment course remains high, especially in EPTs.^{3,21,22} The low efficacy of ibuprofen or acetaminophen monotherapy coupled with increased adverse effects in the highest-risk patients may represent significant obstacles to investigating the effects of PDA intervention on clinical outcomes, calling for effective treatment strategies. A novel approach under investigation is the combined use of acetaminophen and ibuprofen. Although both drugs inhibit PGE2 production, they have different mechanisms and targets. Therefore, the combination therapy with ibuprofen and acetaminophen may have a more synergistic effect than that of monotherapy for PDA closure.²³ Emerging clinical data on the use of combination therapy for hsPDA suggest that combination therapy is more effective than monotherapy.^{11,14,24} Hochwald et al.¹³ first reported that the efficacy of combined ibuprofen and acetaminophen was compared to intravenous ibuprofen alone. In this small randomized control trial, combination therapy showed increased effectiveness, although the difference in the rate of ductal closure did not reach statistical significance. An observational study by Yurttutan et al.¹² demonstrated that 9 out of 12 (75%) infants who had failed 2 previous cycles of monotherapy had

successful ductal closure with combination therapy. Recently published systematic reviews concluded that combination therapy with ibuprofen and acetaminophen is potentially more effective in inducing DA closure than monotherapy.^{25,26} These studies suggested that combination therapy may be a useful second therapeutic option for monotherapy-resistant hsPDA before surgical ligations. Additionally, Saker et al.¹⁴ reported that significant changes in ductal diameter and ductal velocities were demonstrated only when combination therapy was used as a primary modality. Previous studies have also suggested better treatment efficacy with earlier interventions.^{12,13} One possible explanation for this suggestion is that naïve ductal tissue may have a better contractile response to combination therapy.¹⁴ These results are consistent with our findings. To the best of our knowledge, this is the first report evaluating the closure rate of early combination therapy with acetaminophen and ibuprofen in Korea.

As the gestational age decreases, the failure of spontaneous DA closure increases, affecting 60% to 70% of EPTs.^{9,27} Of those that close, up to 30% will reopen and may then reclose or go on to become hemodynamically significant and require pharmacological or surgical closure.^{28,29} In our study, the rates of spontaneous DA closure were 29.7% and 29.2% in periods I and II, respectively. This finding is consistent with the results of the previous reports.

Ibuprofen monotherapy is the most commonly used therapeutic approach for closure of PDA.^{8,9} It has been reported to successfully close the DA in 60% to 85% of cases. PDA in more premature infants can be more resistant to pharmacological treatment. Lower gestational ages have also been described to be associated with lower efficacy rates of ibuprofen.^{30,31} According to the Korean Neonatal Network (KNN) database,

among very low birth weight infants born at 22 to 29 weeks of gestation between 2013 and 2015, 68.7% of infants with pharmacological treatment for hsPDA were successfully managed with only pharmacotherapy.³² However, in our study, the successful closure rate of ibuprofen monotherapy was 57.7%, which was relatively less than the overall closure rate reported from the KNN database, while the closure rate of combination therapy was 76.5%, which was higher than that reported from the KNN database. Our eligibility criteria focused on infants born at <28 weeks of gestation and a birth weight <1,000 g. The lower closure rate may be associated with the lower gestational age and birth weight of the enrolled infants compared with the results from the KNN.

In this study, ibuprofen was administered rectally. This is because, theoretically, rectal administration is more convenient than oral administration and could reduce stomach irritation.^{33,34} Moreover, rectal administration does not increase the burden on liver metabolism. We used a high-dose regimen of ibuprofen based on the previous study that investigated the use of rectal ibuprofen for PDA closure in preterm infants.³⁵ However, a randomized controlled trial of very low birth weight infants demonstrated that a standard-dose of rectal ibuprofen was as effective as oral ibuprofen for hsPDA closure.³⁶ A more recent pilot study showed that dexibuprofen suppository was as effective and safe as oral ibuprofen for PDA closure.³⁴ Thus, we assume that rectal administration would be as effective as oral administration for PDA closure.

Our study did not show any signal of harm associated with combination therapy. Because acetaminophen and ibuprofen are metabolized via different pathways and acetaminophen does not decrease renal perfusion, it is reasonable to hypothesize that combination therapy with these drugs is unlikely to increase the risk of adverse events.³⁷ Previous studies have demonstrated that the number of adverse effects in combination therapy did not increase.^{11,13} A previously published Cochrane review found that in febrile children, combination therapy significantly reduced fever with no serious adverse events compared to monotherapy with either drug.³⁸ Kimani et al.³⁹ reported that combination therapy as first-line ductal treatment did not increase any adverse effects. Another recent study on the safety of adding oral acetaminophen to ibuprofen in preterm infants weighing <1,000 g also showed no adverse

effects observed.²⁴ Our study yielded similar results. These findings suggest that simultaneous administration of acetaminophen and ibuprofen may be safe, even in EPTs.

We acknowledge the intrinsic limitations of this study. This single-center study included retrospective data, and the number of patients was small. Therefore, this study was not sufficiently powered to assess its safety or effectiveness. The study cohorts were divided on a temporal basis, which may represent a bias even though the baseline features were similar between the study cohorts. We cannot exclude the possibility that unknown differences in clinical practice or changes in medical staff composition may have influenced the outcomes of this study. In addition, we did not include detailed changes in echocardiographic parameters before and after therapy. Furthermore, our study focused on short-term adverse outcomes. Further research is needed to investigate the effect of different strategies for managing PDA on brain function and long-term neurodevelopmental outcomes.

In conclusion, combination therapy with acetaminophen and ibuprofen as first-line therapy for hsPDA resulted in improvements in the successful closure rate without increasing adverse effects in EPTs. These findings suggest that the combination of acetaminophen and ibuprofen may be considered as the first therapeutic option for hsPDA in EPTs, with a high rate of treatment failure after monotherapy. Well-designed prospective clinical trials are essential to recommend the use of combination therapy in EPTs.

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Conflict of Interest

Hye Jung Cho is an editorial board member of the *Perinatology*. No potential conflict of interest relevant to this article

was reported.

Authors' Contributions

Conceptualization: EJK, HJC, DWS; Data curation: all authors; Formal analysis: EJK, HJC, DWS; Investigation: all author; Methodology: EJK, HJC, DWS; Writing-original draft: EJK, HJC, DWS; Writing-review & editing: all authors.

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