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Original Article

Use of combination therapy with acetaminophen and ibuprofen for closure of the patent ductus arteriosus in preterm neonates

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Abstract

Objective: To compare effectiveness and safety of combination therapy (acetaminophen and ibuprofen) to monotherapy (ibuprofen, indomethacin, or acetaminophen alone) in treatment of the patent ductus arteriosus (PDA) in premature neonates.

Methods: This was a retrospective cohort study of neonates admitted to a tertiary-level neonatal intensive care unit. Included neonates were born at <32 weeks gestation and received pharmacotherapy for PDA closure. Based on the primary therapy received, our cohort was divided into the following four groups: indomethacin alone, ibuprofen alone, acetaminophen alone, and ibuprofen and acetaminophen (in combination). Baseline characteristics, effectiveness, safety, neonatal mortality, and morbidities rates between these groups were compared.

Results: One hundred and forty neonates were analyzed; 17 received combination therapy, and 123 neonates received monotherapy: 22 (17.9%) ibuprofen, 29 (23.6%) acetaminophen, and 72 (58.5%) indomethacin. The PDA closure rates were 41.7% for indomethacin, 41.2% for combination therapy, 37.9% for acetaminophen, and 31.8% for ibuprofen (P=0.100). Rates of adverse effects were comparable between the groups.

Conclusion: The rate of ductal closure was not different between combination therapy and monotherapy. The study did not demonstrate any increased adverse effects in the combination group. Future well-designed prospective clinical trials are needed to guide clinical practice.

Keywords: *Combination therapy; Neonates; Patent ductus arteriosus*

The ductus arteriosus is a fetal vascular channel that plays a crucial role in maintaining fetal circulation in utero by shunting blood from the pulmonary circulation to the systemic circulation (1). In preterm neonates, the ductus arteriosus may persist beyond the immediate neonatal transitional period. A persistent patent ductus arteriosus (PDA) can have a profound impact on preterm circulation leading to pulmonary over-circulation and systemic hypo-perfusion subsequently contributing to significant morbidity (2,3), although a causal relationship has not been well established. The most common therapeutic approach to hemodynamically significant PDAs is pharmacotherapy using nonsteroidal, anti-inflammatory drugs (NSAIDs) such as indomethacin or ibuprofen (2,4), which have an efficacy rate ranging between 60 and 80%. NSAIDs decrease prostaglandin production through inhibition of the prostaglandin H_2 synthetase enzyme complex at the cyclooxygenase site, thereby inducing ductal closure (3).

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In the last decade, acetaminophen has emerged as therapy for PDA closure. While the exact mechanism of action is unknown, it is postulated that acetaminophen acts via inhibition of the peroxidase site of the prostaglandin H_2 synthetase enzyme complex. This inhibition reduces the amount of prostaglandin G_2 available for conversion to prostaglandin H_2, the precursor of prostaglandin E_2 (which is the predominant circulating prostaglandin that is responsible for maintaining ductal patency) (5,6). However, the acetaminophen-induced reduction in PGH2 production can be counteracted by lipid peroxides and PGG2 itself (7–9). The maturational difference in lipid hydroperoxide production in premature neonates in addition to possible site-specific differences in its levels may contribute to acetaminophen-induced ductal closure, though evidence in neonatal population is lacking (7–9). Despite lack of consensus on its exact mechanism of action, acetaminophen has shown comparable results to NSAIDs when used for ductal closure (3,10–12).

Due to inhibition of different sites on the prostaglandin enzyme system, there has been speculation that these drugs used in combination may be more effective than when used as monotherapy (13). This biological rationale has led to some neonatologists using this combination therapy as first line in PDA treatment in premature neonates. However, to date, there is a lack of robust data regarding the effectiveness of combination therapy for PDA treatment as a first-line strategy. Additionally, safety of such combination therapy also needs to be reviewed. Hence, we conducted the present study to compare the effectiveness and safety of combination therapy with monotherapy for primary PDA closure in preterm neonates.

METHODS

Study design and patient selection

This was a retrospective cohort study including neonates admitted to a tertiary-level neonatal intensive care unit (NICU) in Southwestern Ontario, Canada. Neonates born at ≤32 weeks gestation, who received pharmacotherapy for PDA in the NICU between January 1, 2012 and December 31, 2017 were included. Infants with chromosomal abnormalities, significant congenital malformations, and complex congenital heart disease beyond atrial septal and ventriculoseptal defects were excluded. Ethical approval was obtained from the Institution's Research and Ethics Board (Project ID: 111535).

Neonates who fulfilled eligibility criteria were identified from the local database where neonatal mortality and morbidity data are collected and submitted to the Canadian Neonatal Network. Based on the medication received for the first course for PDA treatment, our cohort was divided into the following four groups: group 1—indomethacin, group 2—ibuprofen, group 3—acetaminophen, and group 4—ibuprofen and acetaminophen. The standard dosing regimens used were defined as: (a) Indomethacin—three doses administered intravenously every 24 hours as 0.2 mg/kg/dose for each dose, (b) ibuprofen—3 doses administered orally every 24 hours as 10 mg/kg for the first dose, then 5 mg/kg for the second and third doses, (c) acetaminophen—28 doses administered orally as 15 mg/kg/dose every 6 hours for 7 days, and (d) combination therapy of ibuprofen and acetaminophen—a course of ibuprofen and acetaminophen as described above given concurrently. Other regimens used were collected as alternative regimens, and details on the doses, routes, and durations used were collected.

Outcomes

We assessed the rate of treatment success after the first course of medical therapy. We defined treatment success as either echocardiographic demonstration of ductal closure and/or echocardiographic demonstration of resolution of hemodynamic significance of PDA and/or no further need for therapy (medical/surgical) for hemodynamically significant PDA for the entire duration of the NICU stay. The features of hemodynamic significance collected based on echocardiography were the following: PDA size—small, moderate, or large; shunt characteristics—restrictive or unrestrictive; left atrium to aortic root ratio of >1.6; diastolic turbulence (back flow in the main pulmonary artery); ductal diameter >1.5 mm; reverse end diastolic flow in the descending aorta; reverse end diastolic flow in the superior mesenteric artery.

To assess adverse effects, we analyzed nephrotoxicity, hepatotoxicity, thrombocytopenia, spontaneous intestinal perforation, and necrotizing enterocolitis in the time period between initiation of therapy and 7 days post the last dose of PDA treatment. We recorded the highest level of creatinine, highest alanine transferase level (ALT) and lowest platelet count in the predefined time period. We defined nephrotoxicity as documented serum creatinine of >100 μmol/L. Hepatotoxicity was defined as an elevation in the liver enzymes of more than twice the upper limit of normal. Necrotizing enterocolitis was defined using the Modified Bells Criteria (14). Severe thrombocytopenia was defined as platelet count <50×10*9/L (15).

We also reported neonatal mortality and short-term morbidities in the cohort; these included intraventricular hemorrhage as defined by Papille (16), bronchopulmonary dysplasia as defined by the National Institutes of Child Health and Human Development (NICHD) consensus definition (17), and retinopathy of prematurity as defined and classified in the International Classification of Retinopathy (18). Sepsis was based on a positive blood, urine or cerebrospinal fluid culture.

Statistical methods

Descriptive data were generated using medians and interquartile ranges (IQR) for continuous variables, and frequencies and percentages for categorical variables. Baseline characteristics, effectiveness, safety, and rates of neonatal mortality and

morbidities between treatment groups were compared using Kruskal–Wallis tests and chi-square tests for continuous and categorical variables, respectively. P-values <0.05 were considered significant.

RESULTS

After reviewing the database, 140 eligible neonates were identified. In this cohort, 17 neonates received combination therapy with ibuprofen and acetaminophen (ibuprofen oral=13, intravenous=4), whereas 123 received monotherapy. Of the 123 neonates who received monotherapy, 72 (58.5%) received indomethacin (intravenous), 22 (17.9%) received ibuprofen (intravenous=10, oral=12), and 29 (23.6%) received acetaminophen (oral).

Baseline characteristics

Baseline characteristics are described in Table 1. There were significant statistical differences between groups for the type of gestation (single versus multiple gestation), mean airway pressure at the onset of treatment and restrictive type of ductal shunts on echocardiography. Neonates receiving indomethacin were more likely than the other groups to be multiples (n=34, 47.0%, P=0.019). The type of ventilator support at the onset of treatment (invasive versus noninvasive) was not significantly different between the groups.

One hundred and twenty-seven (90.7%) neonates had an echocardiography completed at the onset of treatment. The remaining 13 neonates were treated based on clinical diagnosis. No neonates received prophylactic NSAIDs. The most predominant finding was a moderate sized PDA in 74 (57.8%) neonates. The neonates receiving acetaminophen were significantly more likely to have echocardiographic findings of a restrictive PDA relative to the other groups (P=0.006). There were no other significant differences in baseline characteristics.

Treatment strategies, efficacy, and adverse effects

After the first course of treatment, 55 neonates (39.0%) had successful PDA closure. The onset of treatment ranged from day 1 to 34 of life with a median (IQR) of 7 (4, 10) days. PDA closure was confirmed by echocardiography in 18 neonates (33.0%). In the other 37 neonates, treatment success was defined clinically.

Table 2 summarizes the rates of treatment effectiveness and adverse effects in the four treatment groups. Indomethacin had the highest rate of PDA closure at 41.7%, followed by combined therapy of ibuprofen and acetaminophen at a rate of 41.2%. Acetaminophen had a PDA closure rate of 37.9%, and ibuprofen had the lowest rate at 31.8%. The rate of closure, however, was not significantly different between the treatment strategies (P=0.100).

The majority of neonates who received the first course of treatment did not have prespecified adverse effects (n=112, 80.0%). There was no difference between the groups in terms of nephrotoxicity, hepatotoxicity, severe thrombocytopenia, spontaneous intestinal perforation, or necrotizing enterocolitis. Data on the rate of short-term neonatal morbidities and mortality were not significantly different between the four treatment groups (Table 2).

DISCUSSION

Our study reports the use of combination therapy with ibuprofen and acetaminophen as a primary treatment strategy for PDA. We found no significant difference in the effectiveness of combination therapy when compared with monotherapy with indomethacin, ibuprofen, or acetaminophen alone for PDA closure. The lack of statistical significance could be attributed to the small sample size (N=140 neonates) and the small number of patients in the combination group. There is currently an ongoing randomized controlled trial exploring the role of this therapy (https://clinicaltrials.gov/ct2/show/NCT03103022). In a study published by Hochwald et al. (19), the efficacy of combined intravenous ibuprofen and intravenous acetaminophen was compared to intravenous ibuprofen alone. In this small randomized control trial, although combination therapy showed increased effectiveness, the difference in the rate of ductal closure did not reach statistical significance (83% versus 42%, P=0.08). Yurttutan et al. reported the successful use of combination therapy with oral ibuprofen and oral acetaminophen in 9 out of 12 infants who had failed two previous cycles of pharmacotherapy (20).

Our study did not show any significant increase in adverse effects with combination therapy. However, data regarding hepatotoxicity were available in only a small proportion of the cohort (29%). We did not have a standardized definition of nephrotoxicity and did not use a gestational age based cut off for serum creatinine. We also did not have data regarding gastrointestinal bleeding, and the threshold of severe thrombocytopenia was chosen on the basis of clinical practice (15). The lowest platelet count in the post-treatment period was noted in the ibuprofen monotherapy group. Thrombocytopenia and adverse platelet dysfunction are listed as adverse effects of ibuprofen use in premature neonates (21,22). Van Overmeire et al., however, reported no difference in platelet counts between ibuprofen and indomethacin used for PDA (23). El Farrash et al. when comparing oral paracetamol and oral ibuprofen did not report a difference in post-treatment platelet levels (24). Interestingly, the combination group did not have significantly low platelet counts despite the exposure to ibuprofen. Pretreatment platelet levels may have been a potential confounder that was not analyzed in the present cohort.

Table 1. Baseline characteristics across treatment groups

	Indomethacin N=72	Ibuprofen N=22	Acetaminophen N=29	Ibuprofen and acetaminophen N=17	P value
Gestational age (weeks) Median (IQR)	26.0 (24.7, 27.5)	25.7 (24.9, 27.6)	25.7 (24.3, 27.4)	26.1 (25.2, 26.8)	0.929
Birth weight (grams) Median (IQR)	825 (690, 1,042)	790 (642, 980)	880 (715, 1,090)	800 (685, 1,025)	0.540
Age at the start of the treatment course (days)					
Median (IQR)	7 (4,9)	6.5 (3, 12.5)	7 (4,11)	7 (4,10)	0.985
0–7 days (%)	44 (61.1)	13 (59.1)	18 (62.1)	10 (58.8)	0.964
8–14 days (%)	21 (29.2)	5 (22.7)	8 (27.6)	5 (29.4)	
15–28 days (%)	6 (8.3)	3 (13.6)	3 (10.3)	2 (11.8)	
>28 days (%)	1 (1.4)	1 (4.5)	0	0	
Sex Male (%)	38 (52.8)	11 (50.0)	16 (55.2)	6 (35.3)	0.578
Multiple Gestation (%)	34 (47.2)	5 (22.7)	7 (24.1)	3 (17.6)	**0.019**
Mode of delivery					
Vaginal (%)	36 (50.0)	6 (27.3)	14 (48.3)	9 (52.9)	0.268
C-section (%)	36 (50.0)	16 (72.7)	15 (51.7)	8 (47.1)	
Antenatal Steroids*					
ANY (%)	57 (79.2)	19 (86.4)	24 (82.8)	13 (76.5)	0.864
Complete (%)	40 (70.2)	11 (57.9)	16 (66.7)	11 (84.6)	0.445
Apgar Scores, Medians					
5 min	6	6	6	6	0.826
10 min	7	6	7	7	0.526
Surfactant one dose (%)	51 (70.8)	13 (59.1)	25 (86.2)	10 (58.8)	0.078
More than one dose (2+ doses)	19 (26.4)	7 (31.8)	2 (6.9)	4 (23.5)	
Ventilator Support at Treatment onset					
Noninvasive (%)	9 (12.5)	3 (13.6)	3 (10.3)	1 (5.9)	0.918
Invasive	63 (87.5)	19 (86.4)	26 (89.7)	16 (94.1)	
Mean Airway Pressure, Median (IQR)	8.0 (6.5, 9.0)	10.0 (8.7, 12.0)	8.2 (6.0, 10.7)	9.2 (7.1, 12.0)	**0.002**
FiO2, Median (IQR)	0.26 (0.21, 0.35)	0.28 (0.23, 0.35)	0.26 (0.22, 0.32)	0.28 (0.23, 0.37)	0.488
Echo Characteristics Prior to Therapy†					
Echo available pretreatment, n (%)	68 (94)	17 (77.3)	25 (86.2)	17 (100)	
PDA size					
Small	4 (5.9)	1 (5.9)	2 (8.0)	0	0.886
Moderate	41(60.3)	6 (35.3)	15 (60.0)	10 (58.8)	0.299
Large	23 (33.8)	10 (58.3)	8 (32.0)	7 (41.2)	0.252
PDA shunt					
Restrictive	3 (4.4)	0	6 (24.0)	0	0.006
Unrestrictive	13 (19.1)	2 (11.1)	3 (12.0)	4 (23.5)	0.680
No shunt data	52 (76.5)	15 (88.2)	16 (64.0)	13 (76.5)	

IQR Interquartile range; PDA Patent ductus arteriosus.

*,† Missing data in these fields; frequency is based on available data.

Table 2. Efficacy and adverse effects of first course of PDA therapy

	Indomethacin N=72	Ibuprofen N=22	Acetaminophen N=29	Ibuprofen and acetaminophen N=17	P value
Efficacy					
Overall Efficacy	30 (41.7)	7 (31.8)	11 (37.9)	7 (41.2)	0.100
Echo confirmed Closure (%)	12 (40.0)	1 (14.3)	4 (36.4)	1 (14.3)	
Clinically determined closure	18 (60.0)	6 (85.7)	7 (63.6)	6 (85.7)	
Need for PDA ligation (%)	5 (6.9)	2 (9.1)	0	0	0.311
Adverse effects					
Nephrotoxicity *					
Data Available, n (%)	62 (86.1)	18 (81.8)	15 (51.7)	14 (82.3)	
Creatinine, Median (IQR)	70.5 (59.0, 91.0)	57.5 (49.3, 75.0)	72.0 (53.0, 85.0)	66.5 (53.5, 83.8)	0.295
Creatinine Level>100 μmol/L, n (%)	10 (16.1)	3 (16.7)	0	2 (14.3)	0.437
Hepatotoxicity*					
Data Available (%)	5 (6.9)	5 (22.7)	12 (41.3)	7 (41.2)	
ALT, Median (IQR)†	7.0 (5.5, 18.0)	10.0 (7.0, 13.0)	10.0 (7.5, 20.8)	7.0 (6.0, 13.0)	0.786
Thrombocytopenia*					
Data available, n (%)	68 (94.4)	21 (95.4)	26 (89.6)	17 (100)	
Lowest platelet count median (IQR)	208.5 (152.0, 290.8)	94.0 (56.0, 204.5)	138.0 (90.8, 248.8)	205.0 (136.0, 270.5)	0.006
Platelet count <50×10*9/L, n (%)	4 (5.9)	4 (19.0)	3 (11.5)	0	0.126
SIP, n (%)	1 (1.4)	2 (9.1)	2 (6.9)	1 (5.9)	0.616
NEC, n (%)	9 (12.5)	0	2 (6.9)	1 (5.9)	0.286
No adverse effects, n (%)	61 (64.7)	16 (72.7)	21 (72.4)	14 (82.4)	0.426
Neonatal Mortality and Morbidity					
Sepsis	13 (18.1)	7 (31.8)	9 (31.0)	1 (5.9)	0.115
BPD	39 (54.2)	15 (68.2)	14 (48.3)	10 (58.8)	0.537
IVH	36 (50.0)	11(50.0)	16 (55.2)	8 (47.1)	0.952
ROP	33 (45.8)	11 (50.0)	13 (44.8)	9 (52.9)	0.947
Death prior to NICU discharge	7 (9.7)	4 (18.2)	3 (10.3)	1 (5.9)	0.651

ALT Alanine Amonitransferase; BPD Bronchopulmonary dysplasia; IQR Interquartile range; IVH Intraventricular hemorrhage; NEC Necrotizing enterocolitis; NICU Neonatal intensive care unit; PDA Patent ductus arteriosus; ROP Retinopathy of prematurity; SIP Spontaneous intestinal perforation.

*Calculations based on number of patients who had this variable reported.

†No patient had ALT levels more than twice the upper limit of normal.

Commonly, a threshold of 50×10*9/L is considered clinically relevant with regard to increased risk of bleeding and the need for platelet transfusions (15). We did not detect a statistically significant difference when comparing the proportion of neonates with platelet counts below this threshold. Thus, while the preliminary finding of no evidence of increased adverse effects is encouraging, more evidence in larger prospective cohorts is required before recommending clinical use.

We reported an overall low rate of effectiveness at 39% for the first course of medical therapy of PDA. This rate, while being similar to that reported by some studies (19,25,26), is nonetheless lower than the overall closure rate reported of 67% (2,856 of 4,256 infants) published in a recent meta-analysis on therapeutic interventions for hemodynamically significant ductal closure (4). Postnatal age at onset of treatment has been found to be an important contributor to the success of PDA treatment (9,23). Our cohort had a range of treatment from day 1 to day 34 of life with a median of 7 days. Possibly, due to our small sample size, stratification by postnatal age did not reveal any significant difference in the groups. This would be an important

consideration in future prospective studies. Lower gestational ages have also been described to be associated with lower NSAIDs efficacy rates (27); this has been suggested to be due to altered sensitivity of the ductal tissue to nitric oxide (28) and increased prostaglandin sensitivity (29).

Our definition of treatment success was based on either echocardiographic findings or clinical definition (no need for further treatment). The majority of the neonates (n=127, 90.7%) had echocardiographic assessment of their PDA prior to treatment. However, less than half (n=66, 47.1%) had an echocardiographic assessment at the end of the treatment course. The lack of post-treatment echocardiography to define treatment success is a limitation of the present study and a potential source of information bias. However, our clinical definition of treatment success represents a pragmatic approach that is widely adopted by many neonatal centres where post-treatment echocardiography may not always be available.

We acknowledge other limitations of our study, such as the small sample size, which precluded the ability to run a multivariable regression analysis for potential confounding variables that may have explained the significant differences found in the baseline characteristics (multiple gestation, mean airway pressure, and restrictive PDA). There was also lack of a standardized approach to diagnose and confirm PDA treatment success. Short-term morbidities were collected over the duration of the NICU and not temporally associated with the completion of PDA treatment. We could, therefore, not control for this potential source of confounding, which would be an important consideration in a prospectively designed study. However, our study is the first of its kind to describe the use of this particular combination therapy as primary/first-line ductal treatment and compare it to other standard monotherapy strategies.

CONCLUSION

We conclude that primary ductal treatment with a combination of ibuprofen and acetaminophen was comparable to monotherapy with other standard agents without any increased adverse effects. Well-designed, large prospective controlled trials that address safety and efficacy are needed before clinical recommendations can be made regarding the use of combination therapy as first-line treatment for PDA.

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References

1. Gournay V. The ductus arteriosus: physiology, regulation, and functional and congenital anomalies. Arch Cardiovasc Dis 2011;104(11):578–85.
2. Evans N. Preterm patent ductus arteriosus: A continuing conundrum for the neonatologist? Semin Fetal Neonatal Med 2015;20(4):272–7.
3. Benitz WE, Bhombal S. The use of non-steroidal anti-inflammatory drugs for patent ductus arteriosus closure in preterm infants. Semin Fetal Neonatal Med 2017;22(5):302–7.
4. Florez ID, Tamayo ME, Zea AM, et al. Association of placebo, indomethacin, ibuprofen, and acetaminophen with closure of hemodynamically significant patent ductus arteriosus in preterm infants. JAMA. 2018;319(12):1221.
5. Ohlsson A, Walia R, Shah SS. Ibuprofen for the treatment of patent ductus arteriosus in preterm or low birth weight (or both) infants. Cochrane Database Syst Rev 2018;9:CD003481.
6. Jasani B, Weisz DE, McNamara PJ. Evidence-based use of acetaminophen for hemodynamically significant ductus arteriosus in preterm infants. Semin Perinatol 2018;42(4):243–52.
7. Allegaert K, Anderson B, Simons S, van Overmeire B. Paracetamol to induce ductus arteriosus closure: Is it valid? Arch Dis Child 2013;98(6):462–6.
8. Sunil B, Patel S, Girish N. IV Paracetamol for closure of patent ductus arteriosus in preterm neonates admitted to a tertiary care centre. Int J Contemp Pediatr. 2018;5(2):294.
9. Jóźwiak-Bebenista M, Nowak JZ. Paracetamol: Mechanism of action, applications and safety concern. Acta Pol Pharm 2014;71(1):11–23.
10. Singh Y, Gooding N. Paracetamol for the treatment of patent ductus arteriosus in very low birth weight infants. J Neonatal Biol. 2016;5(3):100e116.
11. Terrin G, Conte F, Oncel MY, et al. Paracetamol for the treatment of patent ductus arteriosus in preterm neonates: A systematic review and meta-analysis. Arch Dis Child Fetal Neonatal Ed 2016;101(2):F127–36.
12. Yang B, Gao X, Ren Y, Wang Y, Zhang Q. Oral paracetamol vs. oral ibuprofen in the treatment of symptomatic patent ductus arteriosus in premature infants: A randomized controlled trial. Exp Ther Med 2016;12(4):2531–6.
13. Bardanzellu F, Neroni P, Dessì A, Fanos V. Paracetamol in patent ductus arteriosus treatment: Efficacious and safe? Biomed Res Int 2017;2017:1438038.
14. Lee JS, Polin RA. Treatment and prevention of necrotizing enterocolitis. Semin Neonatol 2003;8(6):449–59.
15. Resch E, Hinkas O, Urlesberger B, Resch B. Neonatal thrombocytopenia-causes and outcomes following platelet transfusions. Eur J Pediatr 2018;177(7):1045–52.
16. Papile LA, Burstein J, Burstein R, Koffler H. Incidence and evolution of subependymal and intraventricular hemorrhage: A study of infants with birth weights less than 1,500 gm. J Pediatr 1978;92(4):529–34.
17. Ehrenkranz RA, Walsh MC, Vohr BR, et al.; National Institutes of Child Health and Human Development Neonatal Research Network. Validation of the National Institutes of Health consensus definition of bronchopulmonary dysplasia. Pediatrics 2005;116(6):1353–60.
18. Quinn GE. The international classification of retinopathy of prematurity revisited: An international committee for the classification of retinopathy of prematurity. Arch Ophthalmol. 2005;123(7):991–9.
19. Hochwald O, Mainzer G, Borenstein-Levin L, et al. Adding paracetamol to ibuprofen for the treatment of patent ductus arteriosus in preterm infants: A double-blind, randomized, placebo-controlled pilot study. Am J Perinatol 2018;35(13):1319–25.
20. Yurttutan S, Bozkaya A, Hüdayioglu F, Oncel MY. The effect of combined therapy for treatment of monotherapy-resistant PDA in preterm infants. J Matern Neonatal Med. 2018;32(21):1–4.
21. Sheffield MJ, Schmutz N, Lambert DK, Henry E, Christensen RD. Ibuprofen lysine administration to neonates with a patent ductus arteriosus: Effect on platelet plug formation assessed by in vivo and in vitro measurements. J Perinatol 2009;29(1):39–43.
22. Olgun H, Ceviz N, Kartal İ, et al. Repeated courses of oral ibuprofen in premature infants with patent ductus arteriosus: Efficacy and safety. Pediatr Neonatol 2017;58(1):29–35.
23. Van Overmeire B, Follens I, Hartmann S, Creten WL, Van Acker KJ. Treatment of patent ductus arteriosus with ibuprofen. Arch Dis Child Fetal Neonatal Ed 1997;76(3):F179–84.

24. El-Farrash RA, El Shimy MS, El-Sakka AS, Ahmed MG, Abdel-Moez DG. Efficacy and safety of oral paracetamol versus oral ibuprofen for closure of patent ductus arteriosus in preterm infants: A randomized controlled trial. J Matern Fetal Neonatal Med 2019;32(21):3647–54.
25. Richards J, Johnson A, Fox G, Campbell M. A second course of ibuprofen is effective in the closure of a clinically significant PDA in ELBW infants. Pediatrics 2009;124(2):e287–93.
26. Louis D, Wong C, Ye XY, McNamara PJ, Jain A. Factors associated with non-response to second course indomethacin for PDA treatment in preterm neonates. J Matern Fetal Neonatal Med 2018;31(11):1407–11.
27. Kluckow M, Lemmers P. Hemodynamic assessment of the patent ductus arteriosus: Beyond ultrasound. Semin Fetal Neonatal Med 2018;23(4):239–44.
28. Chorne N, Jegatheesan P, Lin E, Shi R, Clyman RI. Risk factors for persistent ductus arteriosus patency during indomethacin treatment. J Pediatr 2007;151(6):629–34.
29. Clyman RI, Campbell D, Heymann MA, Mauray F. Persistent responsiveness of the neonatal ductus arteriosus in immature lambs: A possible cause for reopening of patent ductus arteriosus after indomethacin-induced closure. Circulation 1985;71(1):141–5.