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Effects of prophylactic oral ibuprofen on the closure rate of patent ductus arteriosus in premature infants

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Abstract

The aim of this study was to investigate the effects of prophylactic oral ibuprofen on the closure rate of patent ductus arteriosus (PDA).

This was a retrospective study and data on infants born before 36 weeks were collected. The prophylactic group was treated with ibuprofen (10, 5, and 5 mg/kg) from days 1 to 3 after birth, respectively. The conventional group was treated with the same dose of ibuprofen from days 4 to 6 once they were echocardiographically confirmed with PDA on day 3 after birth. The placebo group was treated with 5% glucose.

The closure rate of PDA in the prophylactic group significantly increased on day 7 compared with the placebo group ($P = .02$), but showed no difference compared with the conventional group ($P = .12$). Serum NT-proBNP in the prophylactic and conventional groups decreased compared with the placebo group ($P = .03$ vs $P = .07$).

Prophylactic oral ibuprofen can increase the closure rate of PDA in premature infants; however, it showed no significant advantages compared with conventional treatment. Serum NT-proBNP can be used to observe PDA treatment responses in premature infants.

Abbreviations: AO = aortic root diameter, COX = cyclooxygenase, CRP = C-reactive protein, DA = ductus arteriosus diameter, ELBW = extremely low birth weight, LA = left atrial diameter, LA/AO = left atrial aortic root ratio, LV = left ventricular diameter, NEC = necrotizing enterocolitis, PDA = patent ductus arteriosus, VLBW = very low birth weight.

Keywords: ibuprofen, patent ductus arteriosus, premature infants

1. Introduction

The ductus arteriosus is a channel connecting the pulmonary artery to the proximal descending aorta and is an important route for maternal–fetal exchange. The vast majority of patent ductus arteriosus (PDA) spontaneously closes within 72 hours in full-term infants, and the incidence of PDA is low at approximately 57 per 100,000 live full-term births.[1] The incidence of PDA in premature infants is significantly increased, and the lower the gestational age and birth weight, the higher the likelihood of PDA. Reports show that PDA will occur in approximately 50% of premature infants born before 32 weeks.[2] And 60% to 70% of infants born before 28 weeks require medication or surgery for the treatment of PDA.[3] Persistent PDA in premature infants results in a left-to-right shunt; causes increased pulmonary circulation load, pulmonary edema, and decreased pulmonary compliance; extends mechanical ventilation time and ventilator use[4]; and increases the risk of complications, such as necrotizing enterocolitis (NEC) and prerenal failure.[5] Therefore, active interventions for PDA in premature infants should be performed to decrease the complications and infant mortality rate.

Ibuprofen is a nonselective cyclooxygenase (COX) inhibitor, and studies as early as 1976 have showed that it can be used for the treatment of PDA in premature infants.[6,7] In 2006, the US FDA has approved the use of ibuprofen in the treatment of PDA in premature infants.[8] The conventional ibuprofen treatment of PDA refers to treatment on days 2 to 7 after delivery, particularly on day 3 where ultrasound confirmation or obvious clinical symptoms results in the initiation of treatment. Prophylactic treatment refers to treatment beginning 12 to 24 hours after delivery. Some scholars believe that the closure rate of PDA is higher in extremely low birth weight (ELBW) infants who were treated with ibuprofen earlier, and there were no significant increases in the incidence of side effects in PDA.[9] In addition, some studies also showed that the prophylactic use of ibuprofen can increase the closure rate of PDA, and its side effects were comparable to those of indomethacin; however, there were no significant differences in the long-term therapeutic efficacy, such as mortality rate at age 2 or incidence of neurodevelopmental disorders.[10] Therefore, whether prophylactic use of ibuprofen should be applied requires further investigation. As the spontaneous closure rate of PDA is high, prophylaxis at an earlier stage may increase unnecessary drug exposure in premature infants.[11] Therefore, there is still a great controversy on whether there are advantages to initiating early interventions.

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2. Methods

2.1. Study subjects

Inclusion criteria: This was a retrospective cohort study in the neonatology department of our hospital from December 2014 to November 2015. The study protocol was approved by the Institutional Review Board of Yantai Yuhuangding Hospital. A total of 103 premature infants born before 36 weeks were included in our study. Exclusion criteria: Infants with comorbid ventricular septal defects and other congenital heart diseases, other severe deformities, severe pulmonary hypertension (>50 mm Hg), and coagulation disorders (platelet count of $<50 \times 10^9$/L and symptomatic bleeding) were excluded. The diagnostic criteria for NEC were based on the 2002 guidelines of "Diagnosis and Management of Complicated Intra-Abdominal Infection in Adults and Children" released by the Surgical Infection Society and the Infectious Diseases Society of America. The diagnostic criteria for PDA included as follows: left atrial aortic root ratio (LA/AO) >1.2, ductus arteriosus diameter (DA) >1 mm, and left-to-right horizontal shunt in the ductus arteriosus.[12]

2.2. Experimental design

Clinical data and demographic information were collected by reviewing medical records of the enrolled infants. Subjects were classified into 3 groups: 35 in the prophylactic treatment group, 31 in the conventional treatment group, and 37 in the placebo group. The infants in the prophylactic treatment group were administered oral ibuprofen (10, 5, and 5 mg/kg) on 1, 2, and 3 days after delivery, respectively. In the conventional treatment group, only the infants who were confirmed to have PDA on day 3 after delivery by ultrasound were administered with the same dosage of oral ibuprofen. The placebo group was provided with an equal volume of 5% glucose orally 24 hours after delivery. The patients in the placebo and conventional treatment groups were regrouped on day 3 after delivery based on whether the PDA has closed: spontaneously closure group (n = 49) and nonclosure group (n = 19).

2.3. Main reagents and devices

The Phillips IU22 color ultrasound device was purchased from Royal Phillips of the Netherlands. Ibuprofen suspension (Lot number 101005038) was purchased from Johnson and Johnson Co, Ltd (Shanghai). The NT-proBNP, ET-1, and PGE_2 ELISA kits were purchased from AMEKO (Shanghai).

2.4. Observation markers

Echocardiography was performed on the infants in the 3 groups, 24 hours, 3 days, and 7 days after delivery by cardiac sonographers who did not participate in this study and who have mid-level job titles and extensive ultrasound experience. The parameters measured included as follows: DA, left atrial diameter (LA), left ventricular diameter (LV), and aortic root diameter (AO). Blood samples were obtained from the infants in the 3 groups, 24 hours, 3 days, and 7 days after delivery for C-reactive protein (CRP), urea nitrogen, and creatinine level tests. ELISA reagent kits were used to assess the NT-proBNP, ET-1, and PGE_2 levels. The 24-hour urine volume (mL/kg) and incidence of NEC within 14 days after delivery in the 3 groups of infants were also assessed.

2.5. Statistical analysis

The SPSS 19.0 software was used for the statistical analysis. Qualitative data were compared using chi-squared tests. Quantitative data were presented as means ± standard deviations. The sample mean was analyzed using analysis of variance. $P < .05$ was deemed to be statistically significant.

3. Results

3.1. Basic information

There were no significant differences among the 3 groups in terms of the general status (gestational age, birth weight, and sex composition), blood routine test results (leukocytes, erythrocytes, and platelets), CRP level, renal function (urea nitrogen and creatinine), and 24-hour echocardiography markers (LA, LV, AO, and DA) (Table 1).

3.2. Closure status of PDA

As the age of the infants increased, the PDA closure rate significantly increased. On day 7 after delivery, the prophylactic treatment group had the highest closure rate (97.14%), while the placebo group had the lowest closure rate (78.38%) (Fig. 1).

On day 3 after delivery, the intervention in the prophylactic treatment and placebo groups ended, while that in the conventional treatment group had not yet begun. However, in the conventional treatment group, the PDA of some infants spontaneously closed. At this point, the closure rates for the placebo, prophylactic treatment, and conventional treatment

Table 1

General information of the study subjects.

	Placebo group (n = 37)	Prophylactic treatment group (n = 35)	Conventional treatment group (n = 31)	*P*
Birth weight, g	1479.19 ± 474.80	1452.86 ± 453.16	1507.00 ± 488.88	.60
Age, wk	30.21 ± 1.96	30.97 ± 0.94	30.89 ± 0.75	.34
BUN, mmol/L	5.72 ± 1.99	6.03 ± 1.45	6.15 ± 2.55	.26
Creatinine, μmol/L	92.20 ± 32.07	95.56 ± 30.28	105.73 ± 32.17	.11
WBC, $\times 10^9$/L	15.06 ± 7.87	19.03 ± 9.83	19.13 ± 15.90	.50
Hgb, g/L	190.19 ± 23.51	193.77 ± 22.81	197.55 ± 26.41	.27
Platelet, $\times 10^9$/L	237.30 ± 84.21	231.57 ± 92.88	210.65 ± 78.06	.28
CRP	0.60 ± 1.30	2.60 ± 6.80	1.08 ± 2.30	.10
LV, cm	1.27 ± 0.19	1.30 ± 0.17	1.30 ± 0.19	.48
LA, cm	0.82 ± 0.12	0.85 ± 0.13	0.86 ± 0.17	.34
AO, cm	0.76 ± 0.11	0.74 ± 0.11	0.78 ± 0.12	.82
DA, cm	1.43 ± 0.54	1.57 ± 0.64	1.31 ± 0.62	.18
LA/AO	1.09 ± 0.17	1.16 ± 0.17	1.12 ± 0.20	.29

AO = aortic root diameter, BUN = blood urea nitrogen, CRP = C-reactive protein, DA = ductus arteriosus diameter, LA = left atrial diameter, LA/AO = left atrial aortic root ratio, LV = left ventricular diameter, WBC = white blood cell.

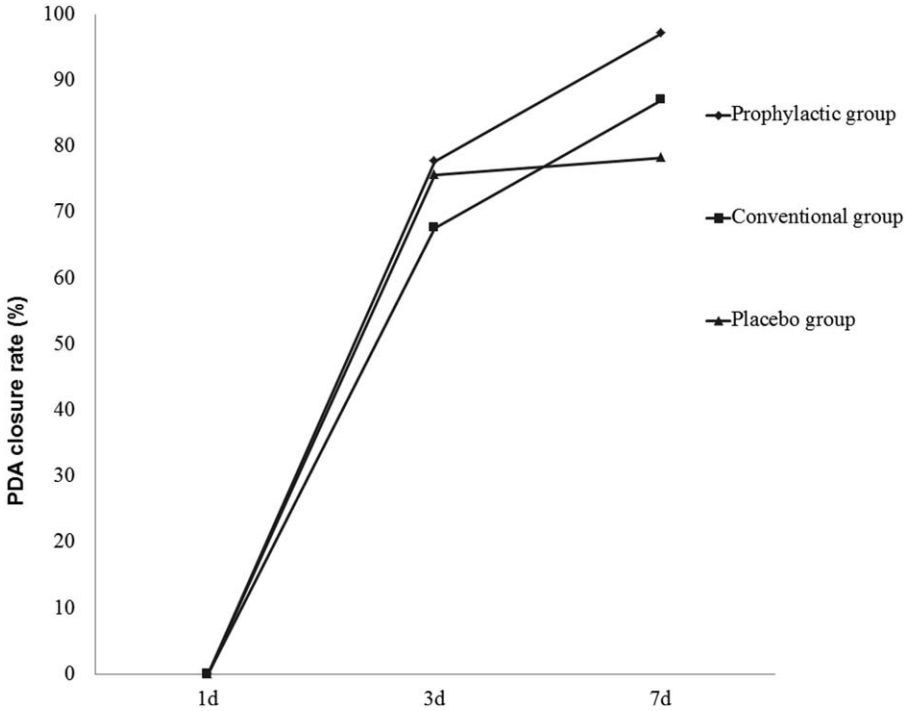

Figure 1. Patent ductus arteriosus closure rate in the 3 groups of premature infants.

groups were 75.68%, 77.78%, and 67.74%, respectively; however, there were no significant differences (Table 2).

On day 7 after delivery, the closure rate of PDA in the prophylactic treatment group significantly increased compared with that in the placebo group, and the difference was statistically significant (97.14% vs 78.38%, $P=.02$). The prophylactic treatment group showed a higher closure rate than the conventional treatment group; however, the differences were not significant (97.14% vs 87.10%, $P=.12$) (Table 2).

3.3. Comparison of the ultrasound markers between the infants with and without spontaneous closure

The infants in the placebo and conventional treatment groups were reclassified into 2 groups based on whether PDA spontaneously closed (n=49) or not (n=19) on day 3 after delivery. We found that there were no significant differences ($P>.05$) in the LV, LA, AO, and LA/AO between both groups 24 hours after delivery; however, there were significant differences in the DA (0.11 ± 0.06 cm vs 0.19 ± 0.06 cm, $P=.00$). The infants with spontaneous closure had a significantly decreased PDA compared with those without (Table 3).

3.4. Adverse reaction status

There were no significant differences in the incidence of oliguria and NEC among the 3 groups. Oliguria was found to be reversible and was alleviated on furosemide administration. There were no significant differences in the urea nitrogen and creatinine levels among the 3 groups on days 3 and 7 (Table 2).

Table 2

Different parameter on days 3 and 7 among different study groups.

	BUN, mmol/L		Creatinine, μmol/L		Closure rate, %	
	Day 3	Day 7	Day 3	Day 7	Day 3	Day 7
Placebo group (n=37)	6.03±2.12	5.32±2.31	96.20±33.64	88.32±29.46	28 (75.68)	29 (78.38)
Phylactic group (n=35)	6.98±1.95	5.71±1.98	106.22±32.48	90.65±31.13	28 (77.78)	34 (97.14)
Conventional group (n=31)	6.33±2.01	5.54±2.06	90.43±35.12	92.74±34.22	21 (67.74)	27 (87.10)
P	.33	.3	.13	.21	.513	.057

BUN = blood urea nitrogen.

Table 3

Echocardiography markers in the spontaneous closure and nonclosure groups.

	LV, cm	LA, cm	AO, cm	LA/AO, cm	DA, cm
Closure group (n=49)	1.26±0.18	0.81±0.12	0.76±0.10	1.06±0.23	0.11±0.06
Nonclosure group (n=19)	1.32±0.20	0.85±0.18	0.77±0.13	1.15±0.18	0.19±0.06
P	.22	.29	.73	.17	.00

AO=aortic root diameter, DA=ductus arteriosus diameter, LA=left atrial diameter, LA/AO=left atrial aortic root ratio, LV=left ventricular diameter.

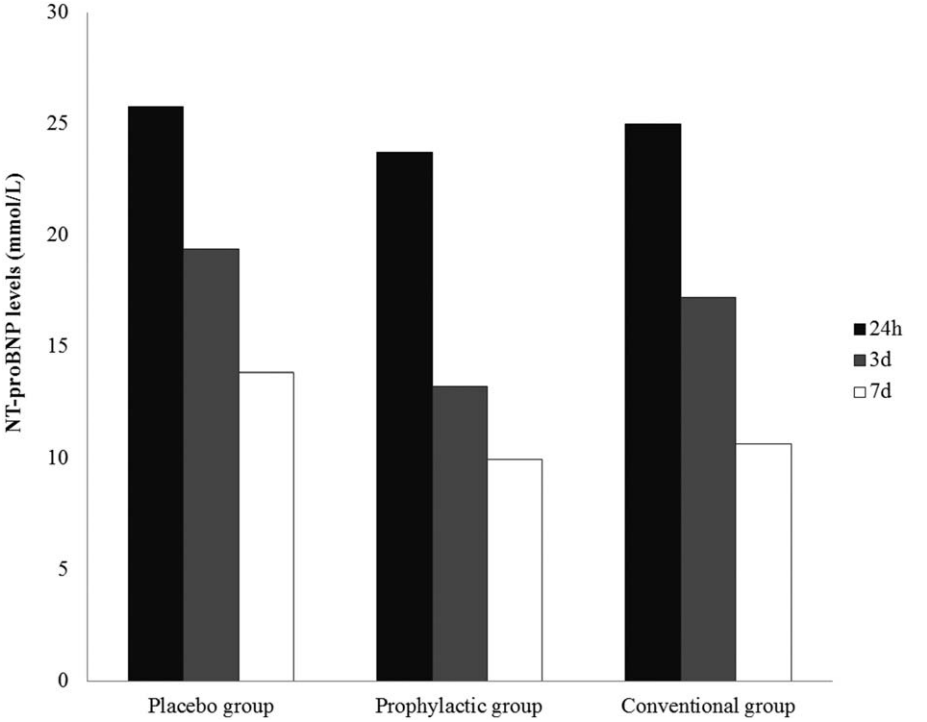

Figure 2. Peripheral blood NT-proBNP levels in the 3 groups of premature infants. Comparison between the placebo group and the prophylactic treatment group.

3.5. Peripheral blood NT-proBNP, ET-1, and PGE_2 levels

There were no significant differences in the 24-hour peripheral blood NT-proBNP levels among the 3 groups ($P > .05$). On days 3 and 7 after delivery, the NT-proBNP levels in the prophylactic treatment group significantly decreased compared with those in the placebo group (13.27 ± 8.29 vs 19.41 ± 10.69, $P = .02$; 9.98 ± 4.14 vs 13.85 ± 7.19, $P = .03$). When the prophylactic treatment group was compared with the conventional treatment group, there were no significant differences in the NT-proBNP levels (Fig. 2).

There were also no significant differences in the peripheral blood ET-1 and PGE_2 levels among the 3 groups 24 hours after delivery (Figs. 3 and 4).

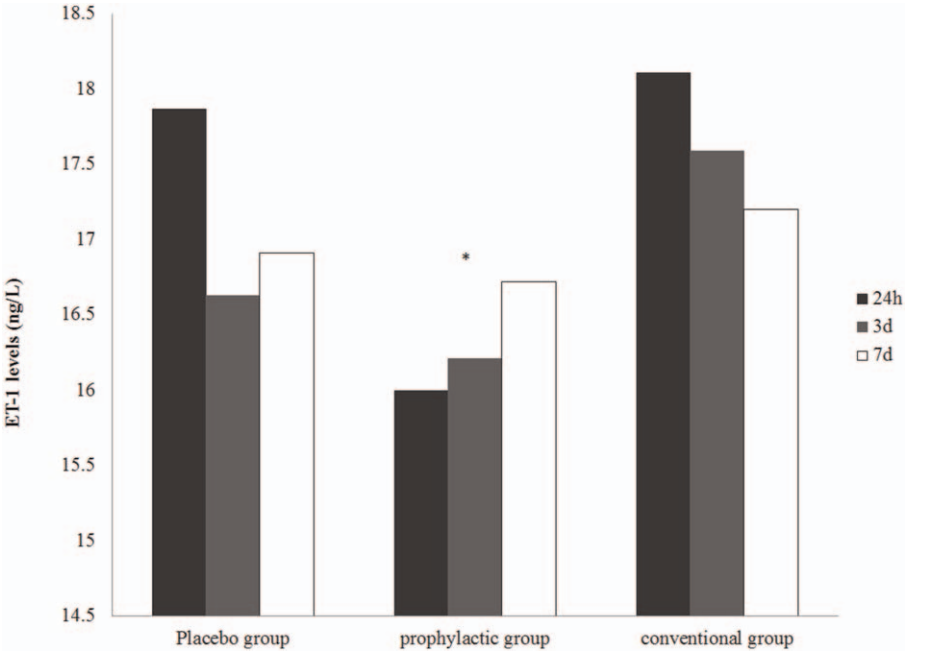

Figure 3. Plasma ET-1 levels (ng/L) in the 3 groups of premature infants.

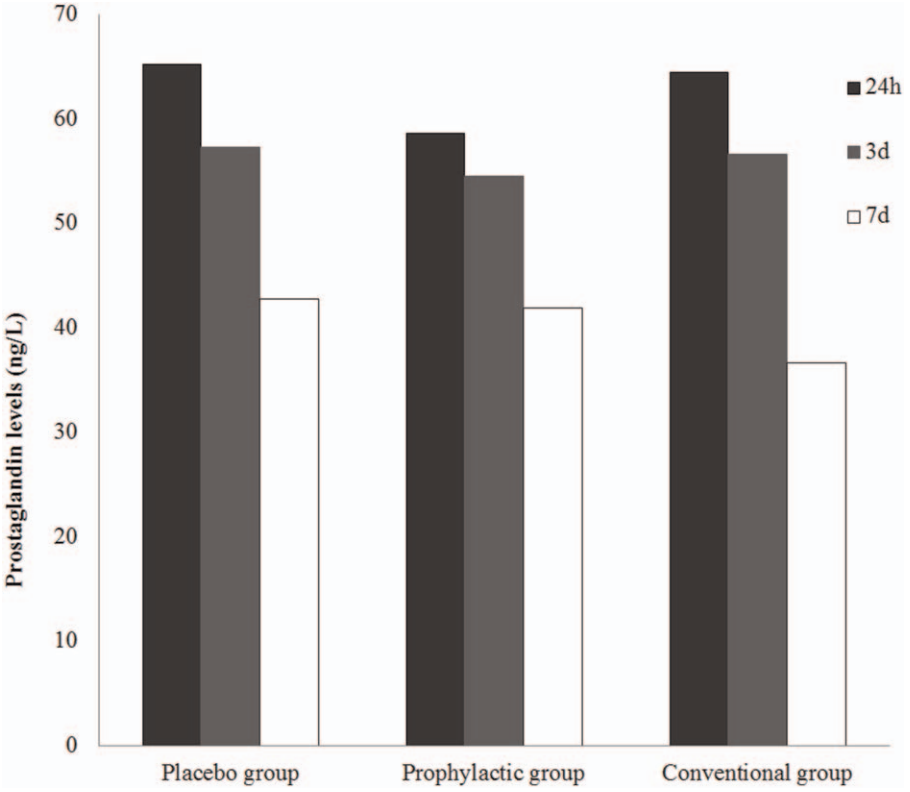

Figure 4. Plasma prostaglandin levels (ng/L) in the 3 groups of premature infants.

Similarly, there were no significant differences in the peripheral blood NT-proBNP and PGE_2 levels between the spontaneous closure group and the nonclosure group within 24 hours after delivery; however, the ET-1 levels in the spontaneous closure group significantly decreased (16.74 ± 6.50 vs 20.65 ± 4.61, $P = .00$) (Fig. 5).

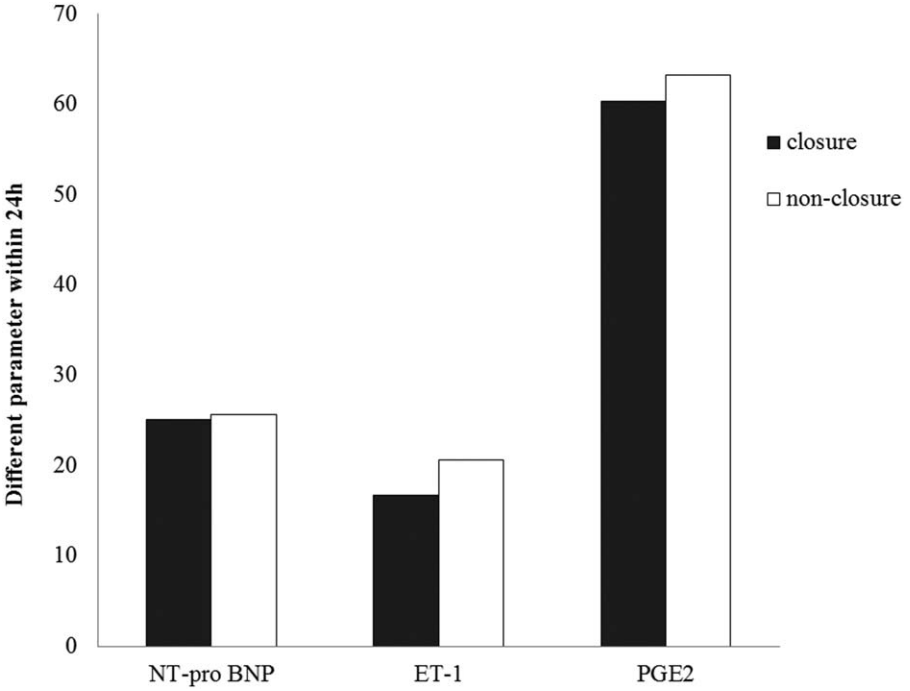

Figure 5. NT-proBNP, ET-1, and PGE_2 levels in the spontaneous closure group and the nonclosure group within 24 hours. Comparison between the placebo group and the prophylactic treatment group.

4. Discussion

4.1. Efficacy and safety of prophylactic ibuprofen in the treatment of PDA in premature infants

The younger the gestational age of the premature infant, the higher the likelihood of PDA occurring. Persistent PDA may increase the mortality rate and incidence of serious complications (e.g., intraventricular hemorrhage, bronchopulmonary dysplasia, NEC) in premature infants.[2,13] Therefore, for premature infants, particularly infants with very low birth weight (VLBW) and ELBW, monitoring and preventing the occurrence of PDA have been extensively paid attention to in clinical practice.

Ibuprofen has started to gain further acceptance by clinicians as a nonselective COX inhibitor in the treatment of PDA. A double-blind, placebo-controlled study that enrolled 135 premature infants younger than 28 weeks found that use of prophylactic ibuprofen significantly decreased the incidence of PDA on day 3 after delivery (28% vs 55%, $P = .0018$); further, all the premature infants in the group did not require surgical ligations, while 6 infants in the placebo group required surgical ligations. This decreased the rate of surgery by 9% ($P = .00277$) but did not decrease the mortality rate.[14] Another study found that prophylactic ibuprofen use can effectively increase the closure rate of PDA in premature infants on day 3 after delivery (60% vs 84%, $P < .001$) and did not affect the incidence of intraventricular hemorrhage (8% vs 9%, relative risk [RR] = 0.97).[15] As ibuprofen does not affect the circulation in the brain, kidneys, and gastrointestinal tract, the likelihood of adverse events due to ischemia in these organs is decreased.[13] Therefore, more clinical studies recently tended to use ibuprofen as a substitute for indomethacin for the treatment of PDA, particularly in neonatal intensive care unit (NICUs) in Europe.

Our experimental results verified the efficacy of prophylactic ibuprofen in the treatment of PDA: The day 7 closure rate of PDA in the prophylactic treatment group significantly increased compared with that in the placebo group, and the difference was statistically significant (97.14% vs 78.38%, $P < .05$). We further verified that ibuprofen use can promote PDA closure in premature infants, which was similar to the findings of previous studies.[16–19] The incidence of short-term complications, such as renal impairment, oliguria, and NEC, in the prophylactic treatment group did not show any significant differences compared with that in the placebo group, showing that prophylactic oral ibuprofen will not increase the incidence of short-term complications. However, as the follow-up period was short, further studies are needed to ascertain whether prophylactic ibuprofen will increase the incidence of long-term adverse events.

At the same time, our experimental results showed that conventional treatment can also increase the PDA closure rate in premature infants; however, the difference was not significant when compared with that in the placebo group (87.10% vs 78.38%, $P > .05$). This was not consistent with the findings of previous studies.[16] An analysis of the reasons for this found 3 possibilities. First, most overseas studies enrolled infants who have VLBW or even ELBW or extremely premature infants who have a gestational age <28 weeks. The possibility of spontaneous PDA closure in these infants is extremely low, and if no intervention is performed, the ductus arteriosus will be persistently opened during the infant stage.[3] However, the premature infants enrolled in our study had a mean gestational age and birth weight of approximately 30 weeks and 1500 g, respectively, and their rate of spontaneous PDA closure was higher. Therefore, this may affect the final results, resulting in the differences between the conventional treatment and placebo groups not showing any statistical significance. Second, the number of patients enrolled was relatively fewer, and the sample size was smaller. This may result in differences not showing statistical significances. If the sample size is increased, and the infants are separated based on their gestational age and birth weight, significant differences may be observed. Third, this is a new treatment strategy with a great controversy as some studies found that the use of high doses of ibuprofen[9,20,21] or use of higher doses of ibuprofen with increasing age[9] can significantly increase the closure rate but not the adverse events. In our study, the time when ibuprofen was administered in the conventional treatment group was relatively later, and the dosage used was consistent with that in the prophylactic treatment group, which was a dose that is currently recognized as a lower dose; this may affect the therapeutic outcomes.

4.2. Prophylactic treatment and conventional treatment

Studies have found that prophylactic intravenous ibuprofen can significantly increase the PDA closure rate on day 3 after delivery but does not show any significant differences with conventional treatment, in addition to no significant differences in adverse events.[22] In addition, the closure rate on day 3 in the prophylactic intravenous ibuprofen group was significantly higher than that in the control group; this decreased the use of indomethacin in later stages.[19] One of our research aims was to evaluate whether prophylactic oral ibuprofen has a better therapeutic efficacy. The results showed that the PDA closure rate in the prophylactic treatment group was higher than that in the conventional treatment group; however, the difference was not statistically significant (97.14% vs 87.10%, $P > .05$), and this was consistent with the findings of a previous study.[22] As the premature infants enrolled in our study had a higher gestational age and birth weight, the spontaneous closure rate was relatively higher, and this may affect the final statistical results. We can further increase the number of patients as well as the number of infants with VLBW and ELBW to compare the differences between the 2 further. As prophylactic medications increase the exposure to drugs in premature infants who experienced spontaneous PDA closure, further evaluation is required on whether prophylactic treatment has advantages.

4.3. DA and PDA

Echocardiography has a significance in monitoring PDA and is the gold standard for its diagnosis. Studies have found that the ductus arteriosus internal diameter is a good predictor of the incidence of PDA requiring therapeutic intervention. This predictive value is better than the LA/AO ratio and volume of the horizontal shunt.[23] It was also found that the condition of patients with a DA > 1.5 mm has a greater likelihood of progressing to symptomatic PDA (sensitivity: 91%; specificity: 100%).[24] Our study compared infants with and without spontaneous closure on day 3 after delivery from both the placebo and conventional treatment groups and found that the DA in the infants in the spontaneous closure group within 24 hours after delivery was significantly smaller than that in the nonclosure group; the difference was statistically significant (0.11 ± 0.06 vs 0.19 ± 0.06, $P < .001$). However, there were no significant differences in the LA/AO ratio, LV, LA, and AO. Therefore, the DA of premature infants within 24 hours after

delivery, which is measured using echocardiography, can be used as a marker for predicting the occurrence of PDA.

4.4. Peripheral blood NT-proBNP, ET-1, and PGE_2 levels and PDA

NT-proBNP can reflect the ventricular capacity load, and its levels can reflect the cardiac function levels in patients with heart failure. Recent studies have found that premature infants with comorbid PDA have significantly higher NT-proBNP levels than those without PDA.[25] The NT-proBNP level and PDA diameter show a positive correlation.[26] The NT-proBNP levels decreased after PDA closure compared with those before closure[27] and decreased to near normal levels after successful PDA treatment with intravenous indomethacin or ibuprofen.[28] Our study found that the PDA closure rate in the prophylactic treatment group was significantly higher than that in the placebo group, and the NT-proBNP levels in the former did not show any significant differences within 24 hours after delivery but significantly decreased on days 3 and 7 compared with those in the placebo group (13.27 ± 8.29 vs 19.41 ± 10.69; 9.98 ± 4.14 vs 13.85 ± 7.19, both $P < .05$). Conversely, there were no significant differences in the PDA closure rate on day 7 after delivery between the conventional treatment and placebo groups. Correspondingly, there were no significant differences in the NT-proBNP levels. Our study found that when the PDA spontaneous closure group was compared with the nonclosure group, there were no significant differences in the NT-proBNP levels 24 hours after delivery. Therefore, we believe that the NT-proBNP levels can reflect the PDA closure status. Patients with a higher closure rate have lower NT-proBNP levels, and this can be used as a marker for monitoring PDA treatment. However, the NT-proBNP level cannot be used for the prediction of PDA occurrence.

ET-1 is an effector of O_2 and plays an important role in the contraction of PDA.[29] Our study found that the spontaneous closure group had significantly lower ET-1 levels 24 hours after delivery compared with the nonclosure group (16.74 ± 6.50 vs 20.65 ± 4.61, $P < .05$); that is, patients with lower ET-1 levels are more prone to spontaneous PDA closure. We speculate that this is because the increase in the left-to-right shunt volume due to PDA increased the pulmonary circulation load, thereby stimulating increased ET-1 synthesis. This causal relationship hypothesis requires further studies for verification as there are currently no similar reports. There were no significant differences in the ET-1 levels among the 3 groups on days 3 and 7 after delivery, suggesting that the ET-1 level cannot be used as a marker to predict PDA conversion after intervention therapy. Nevertheless, the ET-1 level may be used as a biomarker for predicting the occurrence of PDA but will not be helpful for monitoring responses after ibuprofen treatment.

High PGE_2 levels during the fetal stage are an important factor maintaining the patency of the ductus arteriosus, and the PGE_2 levels will decrease after birth, promoting closure of the ductus arteriosus. Studies have found that patients with high plasma PGE_2 levels are more prone to PDA.[30] Our study found that the peripheral blood PGE_2 levels in the 3 groups of premature infants significantly decreased with increasing birth age; however, the pair-wise comparison among the 3 groups at the same point revealed no significant differences. There were also no statistically significant differences between the infants with and without spontaneous closure. These results are not consistent with those of previous studies. Considering that the gestational age of our premature infants was older, which was related to the higher spontaneous closure rate, this characteristic may affect the sensitivity of our results. At the same time, many other factors, such as inflammation, can all affect the synthesis and release of PGE_2. Therefore, the presence of these factors may affect the accuracy and specificity of the results. In conclusion, our results suggest that the PGE_2 level can neither be a predictor of the occurrence of PDA in premature infants nor a biomarker for the response to ibuprofen treatment.

The limitation of this study was that the premature infants enrolled in this study had a higher gestational age, birth weight, and spontaneous closure rate. Under situations of a low sample size, this may affect the results of the study. Owing to time limitations, we were unable to study long-term adverse reactions, such as mortality rate at age 2 or incidence of neurodevelopmental disorders, and determine the long-term efficacy of different ibuprofen regimens. This may be resolved in future studies where we will further refine the classification based on the gestational age and birth weight and focus on enrolling VLBW infants with gestational age younger than 30 weeks and birth weight <1500 g. At the same time, the sample size can be reasonably increased, and the follow-up period could be extended.

Our study found that prophylactic oral ibuprofen can increase the PDA closure rate in premature infants without increasing the incidence of short-term adverse events. However, there were no significant advantages when compared with conventional treatment. The DA 24 hours after delivery in premature infants can be used as an important ultrasonic marker for predicting the occurrence of PDA. The peripheral blood NT-proBNP level can be used as a biomarker for observing the outcomes of PDA treatment in premature infants and the ET-1 level for predicting the occurrence of PDA.

Author contributions

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Writing – original draft: Yanjie Ding, Xiaoliang Wang.
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