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Risk factors for refractory patent ductus arteriosus to initial medical treatment in preterm infants

Aybüke Yazıcı, Hayriye Gözde Kanmaz Kutman, Gülsüm Kadıoğlu Şimşek, Betül Siyah Bilgin, Fuat Emre Canpolat, Şerife Suna Oğuz

Department of Neonatology, University of Health Sciences, Ankara Bilkent City Hospital, Ankara, Türkiye

ABSTRACT

Objectives: This study aims to identify risk factors and clinical markers for refractory patent ductus arteriosus to the initial medical treatment and determine appropriate treatment strategies. The goal is to define the newborns who will respond to treatment and to prevent patients from adverse effects of medical or surgical treatment of patent ductus arteriosus.

Methods: Preterm infants with hemodynamically significant patent ductus arteriosus and whose gestational age was under 30 weeks were retrospectively evaluated. Infants who responded to the initial medical treatment (paracetamol or ibuprofen) were compared to those non-responders. Neonatal characteristics and comorbidities were compared between the groups.

Results: Data from a total of 91 infants were analyzed. The mean gestational age was 27±1.9 weeks vs. 26±1.9 weeks (P=0.10), and birth weight was 1,056±290 vs. 974±318 g (P=0.61), respectively in responder and refractory groups. Success rates for patients treated with paracetamol (n=49) were 57.4%, while for those treated with ibuprofen (n=42), it was 42.6% (P=0.47). Echocardiographic findings such as ductal size 2.48±0.69 vs. 2.55±0.66 mm (P=0.75), and left atrium/aortic root ratio 1.73±0.4 vs. 1.64±0.25, (P=0.14) were also comparable. Incidence of severe intraventricular hemorrhage (22.7% vs 4.3%, P=0.009) and periventricular leukomalacia was significantly higher in the refractory group (53.1% vs. 22.2%, P=0.008).

Conclusions: Combining multiple risk factors into a clinical decision-making model or algorithm could enhance the predictive accuracy of treatment response. Moreover, ongoing monitoring and tailored treatment adjustments based on individual responses and side effects are crucial for effectively managing patent ductus arteriosus in preterm infants.

Keywords: Patent ductus arteriosus, preterm infants, treatment

Patent ductus arteriosus (PDA) is a persistent opening between the pulmonary artery and the descending aorta, a remnant of fetal circulation that typically closes shortly after birth. The ductus arteriosus may remain open in preterm infants, leading to increased pulmonary blood flow and decreased systemic perfusion. The ductus arteriosus is vital to fetal circulation, allowing blood to bypass the fetal lungs. After birth, the initiation of breathing leads to a decrease in pulmonary vascular resistance and an increase in systemic oxygen levels, triggering the functional closure of the ductus arteriosus within the first 24-48 hours in

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Corresponding author: Aybüke Yazıcı, MD., Phone: +90 312 552 60 00, E-mail: aybukeyzc07@gmail.com

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term infants [1-4]. However, in preterm infants, the physiological mechanisms responsible for ductal closure are often immature, resulting in a persistently patent ductus arteriosus. 70% of preterm infants under 28 weeks of gestation require medical or surgical closure of the ductus [1]. Treatment options for PDA include conservative management, pharmacological treatment, surgical ligation, or transcatheter ductal closure, though the optimal treatment strategy remains a topic of debate [5-7]. For PDA treatment, prostaglandin inhibitors, such as indomethacin, ibuprofen, or paracetamol, can be used medically [8]. Surgical ligation of the PDA is considered when pharmacological therapy is unsuccessful or contraindicated [6]. The management of PDA in preterm infants is complex and remains a topic of ongoing debate.

Low gestational age is the strongest risk factor for symptomatic PDA, and many perinatal variables, such as respiratory distress syndrome (RDS), have also been identified as risk factors for symptomatic PDA and poor response to pharmacological treatment [9-11]. PDA continues to be a challenging issue in the care of extremely low birth weight infants [12]. If hemodynamic instability due to PDA is not well managed, it can lead to spontaneous intestinal perforation, necrotizing enterocolitis, intraventricular hemorrhage, impaired renal function, bronchopulmonary dysplasia (BPD), and mortality due to left-to-right shunt impairing gastrointestinal, cerebral, and renal perfusion [8].

The optimal timing and approach for PDA treatment in preterm infants remain controversial. While early intervention may prevent complications associated with a significant PDA, it also exposes infants to the risks of treatment-related adverse effects. There is ongoing debate regarding the long-term outcomes of different management strategies, highlighting the need for further research and well-designed clinical trials. This study aims to identify risk factors for the lack of response to the first course of medical treatment for PDA and to determine appropriate treatment strategies. Thus, it is intended to prevent patients from being exposed to the adverse effects of hemodynamically significant PDA and surgical procedures.

METHODS

Between September 2019 and December 2022, preterm infants with a gestational age ≤ 30 weeks who were monitored in a tertiary neonatal intensive care unit were retrospectively evaluated. The infants were divided into two groups: those who responded to the initial medical treatment either with paracetamol or ibuprofen and those for whom the treatment failed, defined as the refractory group. Factors affecting treatment failure were analyzed. The PDA diagnosis was made based on echocardiography performed at 48-72 hours by a pediatric cardiologist. Hemodynamically significant PDA is diagnosed when the left atrium/aortic root (La/Ao) ratio is >1.5 and/or the ductus diameter is >1.5 mm [15]. Either ibuprofen or paracetamol therapy was administered at the physician's discretion who was giving the primary care. For those whose PDA did not close with medical treatment or for whom medical treatment was contraindicated, surgical ductal ligation was performed. PDA medical treatment failure was defined as the persistence of ductal patency on control echocardiography at the end of medical treatment. The oxygen requirement of the patients was evaluated on postnatal day 28, at 36 weeks postmenstrual age, and at discharge to diagnose BPD [16].

Based on our unit's standard respiratory support protocol, decisions regarding mechanical ventilation or non-invasive support were made, and surfactant was administered due to RDS. Turkish Neonatal Society Guidelines are strictly followed [17]. Cranial ultrasonography (USG) was performed on days 1, 3, and 7, and weekly cranial USG follow-up was conducted based on intraventricular hemorrhage (IVH) findings. IVH was graded according to the Papile classification, with advanced IVH defined as >Grade II [18]. Periventricular leukomalacia was defined based on a central cystic appearance on cranial USG [19]. The necrotizing enterocolitis (NEC) diagnosis was made based on laboratory, clinical, and radiological findings and staged according to the modified Bell criteria [20]. Retinopathy of prematurity (ROP) was staged according to the International Classification of Retinopathy of Prematurity following an examination by an ophthalmologist [21]. Sepsis detected within the first 3 days of life was defined as early neonatal sepsis and sepsis detected after 72 hours was defined as late neonatal sepsis [22]. Enteral and parenteral nutrition were managed according to Turkish Neonatal Society guidelines [23, 24]. Feeding intolerance was defined in the presence of clinical deterioration, abdominal ex-

amination findings (distension, tenderness, increased abdominal circumference, prominent bowel loops, noticeable or absent bowel sounds), vomiting, gastric residuals >50% and/or bloody residuals if checked, and changes in stool frequency [23]. Ethical committee approval was obtained for our study (E2-22-3045).

Statistical Analysis

The data were analyzed using the Statistical Package for Social Sciences (SPSS Inc., Chicago,

IL, USA) for Windows (version 25.0) at a significance level of 0.05. The data were analyzed

using numbers, percentage distributions, mean, and standard deviation. Normality was tested

using kurtosis and skewness coefficients. Pearson's chi-square test and independent samples t-test were used. The Mann-Whitney U test was used for nonparametric data.

RESULTS

Data from a total of 91 infants were analyzed. The mean gestational age in the treatment responder group was 27±1.9 weeks, while it was 26±1.9 weeks in the refractory PDA group (P=0.1). Birth weight was similar between the two groups (1,056±290 g vs. 974±318 g, P=0.61) (Table 1). Preeclampsia was significantly higher in the responders compared to the refractory PDA group (28.3% vs. 9.3%, P=0.03). Neonatal characteristics were similar between the two groups and were represented in Table 1.

Among the patients treated with paracetamol (n=49), the success rate was 57.4%, whereas it was 42.6% in those treated with ibuprofen (n=42); no statistically significant difference was found (P=0.47). Echocardiographic findings were similar between the two groups, such as the ductal size 2.48±0.69 vs. 2.55±0.66 mm (P=0.75) and La/Ao ratio 1.73±0.4 vs. 1.64±0.25 (P=0.14). The incidence of severe IVH and periventricular leukomalacia (PVL) was significantly higher in the refractory PDA group (22.7% vs. 4.3%, P=0.009; 53.1% vs. 22.2%, P=0.008) (Table 2).

Patients with lower admission white blood cell (WBC) and Large Unstained Cells (LUC) values had higher treatment success compared to those with higher values (7300±3697 vs. 9053±6158, P=0.014; 0.42±0.34 vs. 0.67±0.52, P=0.009). Patients with higher interleukin-6 values had better treatment responses than those with lower values (958.5±3131 vs. 178.9±279.9, P=0.009).

DISCUSSION

In this study, we evaluated the risk factors for refractory patent ductus arteriosus to the first course of medical treatment. Responders had higher rates of

Table 1. Demographics of patients by response to initial medical therapy in PDA

	No treatment response (n=44)	Treatment response present (n=47)	P value
Gestational age (weeks)	26 ±1.9	27±1.9	0.1
Birth weight (g)	974±318	1056±290	0.61
Gender (male)	24 (54.5)	22 (46.8)	0.46
Delivery type (CS)	42 (95.5)	45 (97.8)	0.53
Multiple pregnancy	14 (31.8)	15 (31.9)	0.92
Antenatal steroid therapy	20 (76.9)	17 (73.9)	0.8
Clinical chorioamnionitis	3 (7)	0 (0)	0.1
PPROM	8 (18.6)	8 (17.4)	0.88
Preeclampsia	4 (9.3)	13 (28.3)	0.03
Need for resuscitation	14 (32.6)	13 (27.7)	0.61

Data are shown as mean±standard deviation or n (%) where appropriate. CS=Cesarian section, PDA=Patent ductus arteriosus, PPROM=Premature prolonged rupture of membranes

Table 2. Clinical data obtained from patients responding to initial medical therapy in PDA

	No treatment response (n=44)	Treatment response present (n=47)	P value
RDS	38 (86.4)	38 (80.9)	0.47
EOS	14 (31.8)	15 (31.9)	0.99
LOS	40 (90.9)	41 (87.2)	0.57
BPD (moderate-severe)	23 (63,9)	22 (55)	0.43
IVH (grade 3-4)	10 (22.7)	2 (4.3)	**0.009**
PVL	17 (53.1)	8 (22.2)	**0.008**
NEC	9 (23.1)	5 (10.6)	0.12
ROP (3-4)	7 (70)	3 (75)	0.85
Feeding intolerance	20 (57.1)	21 (53.8)	0.77
Invasive mechanical ventilation	22 (50)	19 (40.4)	0.35
Admission FIO_2	38±18	40±19	0.65
Surfactant Dose Count	1.17±0.62	1.36±0.75	0.06
Ibuprofen	22(50)	20 (42.6)	0.47
Treatment application method (intravenous)	17 (89.5)	20 (80)	0.39
Day of treatment (<7 day)	17 (38.6)	10 (21.7)	0.08
Treatment day	5.56±3.39	5.68±7.1	0.43
Number of treatment (≥2)	41 (100)	3 (6.4)	**<0.001**
PDA ligation	19 (46.3)	3 (6.4)	**<0.001**
Ductal diameter	2.55±0.66	2.48±0.69	0.75
La/Ao ratio	1.64±0.25	1.73±0.4	0.14
Urine volume*	3.83±1.35	3.77±1.23	0.65
Mortality	10 (22.7)	7 (14.9)	0.33

Data are shown as mean±standard deviation or n (%) where appropriate. BPD=Bronchopulmonary dysplasia, EOS=Early-onset sepsis, FIO_2=Fractional oxygen concentration, LA/Ao=left atrium/aortic root, LOS=Late-onset neonatal sepsis, IVH=Intraventricular hemorrhage, NEC=Necrotizing enterocolitis, PDA=Patent ductus arteriosus, PVL=Periventricular leukomalacia, RDS=Respiratory distress syndrome, ROP=Retinopathy of prematurity

preeclampsia, lower admission WBC and LUC values, and higher IL-6 levels. Additionally, treatment response was reduced in patients with intraventricular hemorrhage and periventricular leukomalacia.

PDA is common in preterm infants and inversely proportional to gestational age [25]. In a retrospective, multicenter study, out of 842 patients at 23-28 weeks of gestation, 511 received pharmacological treatment for hemodynamically significant PDA. It was found that resistance to repeated medical treatment and the need for surgery were higher in the 23-24-week group. The study emphasized the need for individualized strategies for PDA management in these patients [26]. In our study, no difference was found between the groups regarding gestational age when evaluating the response to PDA treatment.

A previous study found that patients with a history of gestational hypertension had a lower response to indomethacin [27]. However, in our study, patients with a history of perinatal preeclampsia showed a better response to medical treatment. In Lee *et al.*'s [28] study, low gestational age, female sex, maternal pregnancy hypertension, and surfactant use were significant risk factors for symptomatic PDA. Additionally, it was re-

Table 3. Response to first course medical therapy according to hospitalization and laboratory data at the time of PDA diagnosis

	No treatment response (n=44)	Treatment response present (n=47)	P value
WBC (/mm^3)	9,053±6,158	7,300±3,697	0.014
RBC (/mm^3)	4.14±0.69	4.3±0.62	0.66
Hemoglobin (g/dL)	15.5±2.53	16.3±2.1	0.24
Platelets (/mm^3)	234,477±72,930	217,760±61,819	0.31
Delta neutrophil index (%)	4.68±11.1	5.91±9.9	0.83
LUC #	0.67±0.52	0.42±0.34	0.009
MPV (fL)	9.14±0.93	9.46±1.3	0.12
C-reactive protein (mg/L)	0.97±5	0.37±1.07	0.12
Interleukin-6 (pg/mL)	178.9±279.9	958.5±3131	0.009
Procalcitonin (µg/L)	6.17±9.23	5.77±7.54	0.45
Moment of diagnosis blood gas pH	7.23±0.7	7.26±0.6	0.25
Blood gas lactate at the time of diagnosis			
Hemoglobin at diagnosis	12.2±2.45	12.9±2.18	0.64
Platelets at the time of diagnosis	198,777±97,024	165,111±68,821	0.08
MPV at the time of diagnosis	11.1±1.83	10.1±1.56	0.27

Data are shown as mean±standard deviation. WBC=White blood cells, RBC=Red blood cells, MPV=Mean platelet volume, PDA=Patent ductus arteriosus, LUC= Large unstained cells

ported that histological chorioamnionitis and antenatal steroid use reduced symptomatic PDA in infants at 26-29 weeks of gestation. Antenatal steroid administration reduces RDS, which is a strong risk factor for preterm PDA [28]. In our study, rates of RDS, antenatal steroid administration, and clinical chorioamnionitis were similar in the two groups.

Another study found that clinical chorioamnionitis reduced the risk of PDA and noted that the mechanism of clinical chorioamnionitis in PDA closure is complex [29, 30]. Behebodi reported that both clinical and histological chorioamnionitis protects against PDA formation by promoting lung maturation [31].

Harink *et al*. [32] investigated the predictive value of clinical and echocardiographic parameters for deciding on surgical ligation after the failure of medical closure of PDA in preterm infants. In a study involving infants born at less than 37 weeks, surgical ligation was performed on 40 out of 89 patients. It was found that invasive respiratory support, a high La/Ao ratio, and the presence of steal were indicative for deciding on surgical ligation [32]. In our study, the La/Ao ratio and duration of invasive respiratory support were similar between the group that responded to medical treatment and the other group. The fact that our study included more immature infants may explain this difference. In a prospective study conducted on 42 infants born at less than 30 weeks gestational age, it was indicated that at postnatal day 72, an La/Ao ratio greater than 1.4 and a PDA size to weight ratio greater than 3.2 mm/kg had high predictive value for the need for PDA intervention. It was emphasized that serial daily echocardiographic evaluations could provide information on whether PDA closure would be achieved with non-steroidal medication or surgical ligation [33]. Early identification of infants at risk for PDA complications may positively affect treatment outcomes. In a prospective study involving infants born between 22-27 weeks of gestation, high levels of inflammation markers such as IL-6, IL-8, IL-10, and IL-12 were found to be associated with persistent PDA [34]. In our study, IL-6 levels were higher in the group that re-

sponded to treatment compared to the other group. A review has indicated that existing evidence suggests that thrombocytopenia and platelet function disorders contribute to the failure of spontaneous and pharmacological PDA closure in preterm infants [35]. In our study, however, there was no difference in platelet counts between the group that responded to treatment and the other group.

The treatment of PDA after the failure of pharmacological therapy in preterm infants is controversial and shows significant variations in practice [32]. While paracetamol has been found to be as effective as ibuprofen in closing PDA [8] and indomethacin has been found to be more effective than placebo or no treatment [36], recent studies have compared the efficacy and safety of combination therapies with monotherapy [13, 14]. In Kimani *et al*.'s [13] study, involving 140 infants born at less than 32 weeks of gestation, 17 received combination therapy, and ductal closure was found to be similar in the combination and monotherapy groups. Yurttutan *et al*. [14] reported that combination therapy with ibuprofen and acetaminophen was successful in patients who previously had failed ductal closure with medical treatment. When medical treatments fail, surgical methods are preferred, though they carry potential risks. In Park *et al*.'s [37] study, comparing a group undergoing surgery after medical failure with a group undergoing surgery from the outset, the latter group had lower incidences of BPD, NEC, sepsis, and ROP. It was suggested that direct surgery might be more beneficial than waiting for medical treatment to fail. Dani *et al*. [26] noted that although the need for surgical closure after multiple medical treatments was twice as high in immature infants, it is desirable to avoid exposing these infants to the risks of surgery and general anesthesia. Considering these studies, it was thought that applying combination therapy instead of monotherapy could prevent delays in treatment. Our study results showed that patients with IVH and PVL had a higher rate of PDA treatment failure, suggesting that both combination therapy and timely surgical intervention should be considered for these patients. Vaidya *et al*. [38] highlighted that late initiation of medical treatment for PDA (postnatal day 11±8.2) might result in lower closure rates. In our study, treatments were started within the first week in both groups. In Kimani *et al*.'s [13] study, the time to start medical treatment ranged from 1 to 34 days (median 7 days), with a PDA closure rate of 37.9% for acetaminophen and 31.8% for ibuprofen. In our study, the success rate was 57.4% for paracetamol and 42.6% for ibuprofen, which may be attributed to the earlier initiation of treatment compared to Kimani *et al*'s [13] study.

Limitations

Our study's limitations include its retrospective design, being conducted at a single center, and the small number of patients.

CONCLUSION

In the management of PDA, the use of combination therapy instead of medical monotherapy may prevent the loss of time associated with monotherapy failure. Prospective studies designed for this purpose are needed. In cases where elevated WBC, IVH, or PVL are detected, the possibility of medical treatment failure should be considered, and patient-based strategies should be developed.

Ethical Statement

The study was reviewed and approved by the ethics committee of University of Health Sciences, Ankara Bilkent City Hospital (Ethics approval decision no: E2-22-3045 and date: 23.12.2022). All participants signed informed written consent before being enrolled in the study. All procedures were performed according to the Declaration of Helsinki.

Authors' Contribution

Study Conception: AY, HGKK; Study Design: AY, HGKK; Supervision: HGKK, GKŞ, BSB; Funding: N/A; Materials: AY, HGKK, GKŞ; Data Collection and/or Processing: AY, BSB; Statistical Analysis and/or Data Interpretation: AY, HGKK, FEC, ŞSO; Literature Review: AY, HGKK, ŞSO; Manuscript Preparation: AY, HGKK and Critical Review: AY, HGKK, FEC, ŞSO.

Conflict of interest

The authors disclosed no conflict of interest during the preparation or publication of this manuscript.

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