

# The Ideal Timing of Bedside Surgical Ligation of Patent Ductus Arteriosus in Premature Babies Less Than 30 Gestational Weeks

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## What is already known on this topic?

- Hemodynamically significant patent ductus arteriosus frequently seen in preterm babies born before 30 weeks of gestation results in blood flow from the systemic circulation to the pulmonary circulation, causing pulmonary hyperemia and systemic hypoperfusion.
- Cyclooxygenase inhibitors are used in the first line as treatment cycles. They are effective for achievement of ductus arteriosus closure in preterm infants, but surgical ligation is applied in rare cases where pharmacologic treatment is contraindicated or unsuccessful.
- There is still no consensus about the number of pharmacologic treatment cycle failures to wait for before deciding on surgical ligation.

## What this study adds on this topic?

- Prolonging medical treatment in order to avoid surgery increases hospital morbidity and prolongs hospital stay.
- Surgical ligation should be considered in the foreground after the second unsuccessful medical treatment cycle, in order to improve the clinical outcomes of the patients.

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## ABSTRACT

**Objective:** The aim of our study is to determine the relationship between exposure to hemodynamically significant patent ductus arteriosus and morbidities in premature babies, the optimal number of pharmacologic treatment cycles, and ideal ductus ligation timing.

**Materials and Methods:** The study was a retrospective single-center study conducted in a 3-year period between July 2017 and June 2020. Premature babies, born  $\leq 30$  weeks of gestation and transferred to our unit for bedside ductus ligation, were included in the study. The subjects were divided into 2 groups; Group A consisted of the patients who received  $\geq 3$  pharmacologic treatment cycles, and group B consisted of the patients who received  $\leq 2$  cycles. The groups were compared according to preoperative and postoperative features. The main outcome of the study was the presence of severe bronchopulmonary dysplasia. The secondary outcomes were specified as the length of stay in the neonatal intensive care unit and the duration of invasive mechanical ventilation (MV).

**Results:** The study group consisted of 24 patients. There were 10 patients in group A and 14 patients in group B. The mean gestational week and the mean birthweight were found to be  $26.7 \pm 2.2$  weeks and  $928 \pm 190$  g, respectively. The incidence of severe bronchopulmonary dysplasia was significantly higher in group A (70% vs. 14.3%;  $P = .019$ ). Post-ligation invasive MV, duration, and length of stay in the intensive care unit were found to be significantly longer in group A. None of the patients had hemodynamic disturbances or complications during and after the operation.

**Conclusions:** Bedside surgical ductus ligation is a safe procedure. Prolonging pharmacologic treatment in order to avoid surgery increases the risk of severe bronchopulmonary dysplasia and prolongs hospital stay.

**Keywords:** Bedside surgery, patent ductus arteriosus, premature, bronchopulmonary dysplasia

## INTRODUCTION

The ductus arteriosus (DA) is a central vascular shunt connecting the pulmonary artery to the aorta, allowing oxygenated blood from the placenta to bypass the uninflated fetal lungs and enter the systemic circulation. DA is a physiological necessity in the intrauterine life, closes functionally within 72 hours and anatomically within 1 week in term babies, due to the increased ambient oxygen level after birth and the decrease of prostaglandins produced from the placenta.<sup>1</sup> In preterm babies, however, sensitivity to oxygen is low,

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while sensitivity to prostaglandin and nitric oxide is high in the ductal tissue. This reduces the rate of ductal closure and increases the likelihood of reopening after closure. Failure of DA closure, termed patent ductus arteriosus (PDA), is the most common cardiovascular disease in preterm newborns. The ductus remains open at 7 days of age in one-third of infants born between 28 and 30 weeks of gestation, in up to 64% of infants born at 27 to 28 weeks' gestation, and in 87% of infants born at 24 weeks.<sup>2,3</sup> Patent DA closes spontaneously in the first year in 75% of those born below 28 gestational weeks, and until the time of discharge in 94% of those born between 28 and 30 weeks.<sup>2,4</sup> In 60% of these babies, however, PDA is called hemodynamically significant PDA (hsPDA), and persistent ductal shunting results in blood flow from the systemic circulation to the pulmonary circulation, causing pulmonary hyperemia and systemic hypoperfusion. Long-term exposure of the premature baby to hsPDA is associated with mortality and morbidities including necrotizing enterocolitis (NEC), pulmonary hemorrhage, intraventricular hemorrhage (IVH), retinopathy of prematurity (ROP), bronchopulmonary dysplasia (BPD), and poor neurodevelopmental outcomes.<sup>5-7</sup>

This association has encouraged neonatologists to treat PDA in order to reduce these associated morbidities, but there remains a wide variety of management options across neonatal units worldwide.<sup>8,9</sup> A conservative management approach, consisting of fluid restriction, diuretics, and positive end-expiratory pressure or pharmacotherapy with cyclooxygenase (COX) inhibitors used in the first stage as treatment cycles, is effective for PDA closure in preterm infants. In rare cases, where pharmacologic closure or conservative management is contraindicated or unsuccessful, surgical ligation or transcatheter closure of PDA is applied.<sup>10</sup> There is still no consensus about the number of pharmacologic treatment cycle failures to wait for before making a decision for surgical ligation. The general approach is that the responsible clinician chooses surgical or pharmacologic closure according to the infant's status, if 2 cycles of COX inhibitors fail.<sup>11</sup> Since PDA ligation has surgical complications and the long-term prognosis is poor in infants, many clinicians avoid this procedure, regard it as a final option, and give more chance to pharmacologic treatment options. Therefore, the duration of exposure to hsPDA may be prolonged and the frequency and severity of both pulmonary and systemic complications may increase.

The aim of our study is to determine the relationship between hsPDA and morbidities seen in premature babies, the optimal number of pharmacologic treatment cycles, and the ideal PDA ligation timing, based on the patients transferred to our unit for bedside PDA ligation.

## METHODS

### Design and Setting

The study was a retrospective single-center study conducted in a 3-year period between July 2017 and June 2020. Our center is a third level neonatal intensive care unit and a reference hospital for congenital heart surgery. The study was approved by the Ethics Committee of İstanbul Yeni Yüzyıl University (File number: 2066). The study was conducted in accordance with

the Declaration of Helsinki. Informed written consents were obtained from the parents of all participants for surgical and intensive care procedures.

### Study Population

Premature babies born at and below 30 weeks of gestation and transferred to our unit for bedside PDA ligation were included in the study.

### Exclusion Criteria:

- (1) Additional accompanying congenital cardiac anomaly.
- (2) Syndromic or chromosomal disease.

### Data Collection

The data were collected via medical record review. The demographic and preoperative data included gender, birthweight, gestational week, antenatal steroid application status, the need for resuscitation in the delivery room, the need for surfactant and the number of applications, time to detect PDA, pharmacologic treatments applied, number of cycles, and echocardiographic findings. Preoperative IVH, pulmonary hemorrhage, NEC, acute renal failure, and sepsis, which might have been associated with PDA, were recorded. The preoperative invasive mechanical ventilation (MV) time, non-invasive MV time, and free oxygen time were recorded.

### Perioperative Procedures

After admission to the unit, detailed echocardiography was performed in all subjects by a pediatric cardiologist, and ductal characteristics were recorded. Indication for surgery was confirmed with echocardiographic parameters of hsPDA described below plus clinical signs of pulmonary overcirculation (invasive MV dependence) and/or systemic hypoperfusion (hypotension with or without metabolic acidosis).

### Echocardiography

The parameters we use to confirm the presence of hsPDA<sup>12</sup> are PDA diameter  $\geq 2$  mm and/or PDA diameter index (mm/kg)  $>1.4$ , left atrium : aortic root ratio  $>1.4$ , retrograde or absent flow during diastole in the descending aorta.

### Derivation of the Ventilation Index (VI)

Ventilation index scores were calculated as follows:  $VI = ([\text{ventilator respiratory rate}] \times [\text{peak inspiratory pressure} - \text{positive end-expiratory pressure}] \times \text{PaCO}_2) / 1000$ .<sup>13</sup>

The ventilation index was measured in the morning on the day of surgery in order to standardize the respiratory status of the patients. At the end of the operation, respiratory parameters were monitored by ventilation index measurements at the 12th hour, 24th hour, 48th hour, and 72nd hour.

### Surgical Procedure

Patent DA ligation was routinely performed at the bedside in the NICU. During the operation, the ventilation process of the patient was operated by the neonatologist using neonatal-compatible ventilators. Fentanyl IV (10  $\mu\text{g/kg}$ ) was used for general anesthesia and rocuronium bromide (0.3  $\mu\text{g/kg}$  IV) was used as a muscle relaxant. Following the anesthesia,

skin antisepsis was achieved appropriately with iodine. The skin was covered with drape and left posterolateral thoracotomy was performed. The lungs were retracted anteriorly and PDA was explored. Patent DA was ligated with 3-0 silk sutures using single ligation technique. One 8 FR drainage tube was placed in all patients. The ribs were adducted with 2-0 vicryl. The skin was closed separately with 4-0 vicryl continuous sutures.

Postoperative data including surgical complications, invasive MV duration, non-invasive MV duration, free oxygen therapy time, BPD and severity, NEC, ROP, IVH, periventricular leukomalacia (PVL), NICU stay, mortality, and postconceptional week at the time of discharge, were recorded.

### Study Groups

The patients were divided into 2 groups according to the number of pharmacologic treatment cycles they received. Group A consisted of the patients who received 3 or more cycles, and group B consisted of the patients who received 1 or 2 cycles.

### Outcomes

The main outcome of the study was the presence of severe BPD ( $>30\%$   $\text{fiO}_2$  requirement or nasal Continuous Positive Airway Pressure (CPAP) or invasive MV need at postconceptional 36 weeks).<sup>14</sup> Secondary outcomes were specified as length of stay in Neonatal Intensive Care Unit (NICU) and invasive MV duration.

### Statistical Analysis

All statistical analyses were performed using Statistical Package for the Social Sciences (SPSS) version 23 (IBM SPSS Corp.; Armonk, NY, USA). Compatibility with normal distribution was examined using the Shapiro-Wilk test. Bivariate comparisons were performed for demographic and perioperative characteristics of the patients in study groups A and B. Chi-square test was used for comparison of the categorical variables. In comparison of quantitative variables independent *t*-test was used for normally distributed data and Mann-Whitney *U*-test used for non-normally distributed data. The significance level was taken as  $P < .05$ .

## RESULTS

The medical files of 26 patients, who had bedside PDA ligation in the study period, were examined. One patient was excluded from the study because she had trisomy 18 and the other patient, who was a 37-week term baby, was excluded because of accompanying ventricular septal defect. Consequently, the study group consisted of 24 patients, and 45.8% of these patients were female. Nineteen of the patients had type A (conical) PDA, and 5 had type C (tubular) PDA. The mean gestational week and the mean birthweight were found to be  $267 \pm 22$  weeks, and  $928 \pm 190$  g, respectively. All patients were admitted from external centers and at least one pharmacologic treatment cycle had been applied.

The patients were divided into 2 groups according to the number of medical cycles applied before ligation. There were 10 patients in group A ( $\geq 3$  cycles) and 14 patients in group B ( $\leq 2$  cycles). The first choice was intravenous (IV) ibuprofen in 14 patients and paracetamol (7 IV, 3 peroral (PO)) in 10 patients.

One patient in group B was ligated after single-cycle IV ibuprofen due to drug side effect (gastrointestinal bleeding). In the second-cycle preferences, paracetamol was used in 12 patients (10 IV, 2 PO) and IV ibuprofen was used in 11 patients. Of the 10 patients who received third-cycle treatment, 7 received IV ibuprofen (normal dose in 5 patients, high dose 2 patients), and 3 received IV paracetamol.

The demographic, echocardiographic, and pre-ligation clinical characteristics of the groups are compared in Table 1. The median invasive MV duration of the patients in group A was significantly longer compared to that of group B (29.5 days vs. 17 days;  $P = .001$ ). While the median postnatal ligation day in group A was 36.5 days, this value was 17 days in group B ( $P < .001$ ). In the other comparisons, no significant difference was found between the groups.

Preoperative and postoperative ventilator indices (VI), which were examined in order to compare the impairment levels of the respiratory mechanics of the patients, are shown comparatively in Table 2. The VI scores of group A patients were significantly higher compared to group B at all calculation points, both preoperatively and postoperatively, which reflects more impaired respiratory mechanics.

None of the patients had hemodynamic disturbances or complications during and after the operation. The follow-up of 5 patients was carried out by experienced neonatologists after the 3rd postoperative day in the center they were referred from with close communication.

Intensive care follow-ups and clinical features of the subjects after ligation are presented comparatively in Table 3. The incidence of severe BPD, which was the main outcome, was significantly higher in group A (70% vs. 14.3%;  $P = .019$ ). There was no significant difference in mortality, but 2 patients who died (because of nosocomial sepsis) were in group A and their mortalities were unrelated to the ligation procedure (33 and 47 days post-ligation). The post-ligation invasive MV duration, total invasive MV duration, and length of stay in NICU in the patients in group A were found to be significantly longer than for those in group B.

The clinical features are presented in Table 4 according to the main outcome of the study, which was presence of severe BPD. Pre-ligation, post-ligation, and total invasive MV times were significantly longer in patients with severe BPD compared to those without severe BPD. The ligation day of the patients with severe BPD was significantly later. There was no significant difference in terms of the other variables. Since the number of subjects was not sufficient, a suitable multivariate logistic regression model could not be created to determine the independent variable in terms of severe BPD.

## DISCUSSION

Before the widespread use of antenatal corticosteroids, PDA was a condition seen in preterms at any gestational week and was associated with respiratory distress syndrome. While medical closure with indomethacin was the standard, studies on the benefits of early or prophylactic surgical closure were being conducted.<sup>15,16</sup> With the use of antenatal steroids,

**Table 1.** Comparison of Demographic and Pre-ligation Clinical Characteristics of the Groups

	Group A ( $\geq 3$ Medical Treatment Cycles), n = 10	Group B ( $\leq 2$ Medical Treatment Cycles), n = 14	P	
Female gender, n (%)	5 (50)	6 (42.9)	.729	$\chi^2$
Gestational weeks (week), median (min-max)	26 (24-30)	27 (23-30)	.722	U
Birth weight (g), mean $\pm$ SD	847 $\pm$ 161	985 $\pm$ 193	.079	T
Delivery room resuscitation need, n (%)	9 (90)	8 (57)	.081	$\chi^2$
Presence of antenatal corticosteroid use, n (%)	5 (50)	10 (71.4)	.285	$\chi^2$
Surfactant dose number, median (min-max)	2 (1-3)	2 (1-4)	.825	U
Day of PDA diagnosis (day), median (min-max)	5.5 (3-10)	6 (3-14)	.721	U
Pre-ligation invasive MV duration (day), median (min-max)	29.5 (14-40)	17 (13-24)	.001	U
Pre-ligation NEC, n (%)				$\chi^2$
No	5 (50)	9 (64.3)	.332	
Stage 1	1 (10)	3 (21.4)		
$\geq$ Stage 2	4 (40)	2 (14.3)		
Pre-ligation IVH, n (%)				$\chi^2$
No IVH	5 (50)	5 (35.7)		
Stage 1	3 (30)	6 (42.9)	.712	
Stage 2	2 (20)	2 (14.3)		
Stage 3	0	1 (7.1)		
Pre-ligation ARF, n (%)	2 (20)	1 (7.1)	.348	$\chi^2$
Pre-ligation Sepsis, n (%)	5 (50)	4 (28.6)	.285	$\chi^2$
Pre-ligation Pulmonary Hemorrhage, n (%)	1 (10)	1 (7.1)	.803	$\chi^2$
PDA diameter (mm), median (min-max)	2.9 (1.6-4)	2.7 (2.1- 4)	.860	U
LA/Ao ratio	1.50 $\pm$ 0.05	1.48 $\pm$ 0.07	.506	t
Ligation day, Median (min-max)	36.5 (21-56)	17 (13-35)	<.001	U

PDA, patent ductus arteriosus; MV, mechanical ventilation; NEC, necrotizing enterocolitis; IVH, intraventricular hemorrhage; ARF, acute renal failure; LA/Ao, left atrium aortic root ratio;  $\chi^2$ , chi-square test; t, independent samples t test; U, Mann-Whitney U-test.

postnatal surfactant applications, and the development of gentle ventilation strategies, the spontaneous closure rate of PDA reached 98% in preterm babies and PDA rarely required intervention above 30 gestational weeks.<sup>2</sup> Nowadays, PDA management is focused on the most premature infants, in whom the ductus can be resistant to pharmacologic treatment, and pulmonary and systemic effects are more severe due to end organ immaturity.

Despite a large number of trials, research studies, and scientific efforts toward an evidence-based consensus on how best to manage PDA in these vulnerable infants, there has been no agreement on how to treat or even how to assess PDA and its impact in the best way.<sup>17</sup> Different strategies have been studied over the years, including prophylactic treatment, early targeted treatment, treatment of clinically symptomatic PDA, conservative approach, surgical ligation, and percutaneous transcatheter closure.<sup>17-20</sup>

The classical approach in preterm babies with hsPDA detected during the follow-up is conservative management or pharmacologic treatment with COX inhibitors (especially indomethacin, ibuprofen, and paracetamol).<sup>21</sup> Surgical ligation is often the alternative in cases where there is no response to the conservative approach or medical treatment, or there is contra-indication.<sup>10</sup> This is one of the most controversial stages in PDA treatment among clinicians. On the one hand, the group arguing that prolonged PDA exposure increases respiratory and other organ morbidities in preterm babies and that the ductus structure is resistant to medical treatment in babies born below 30 weeks of gestation, recommends a maximum of 2 pharmacologic treatment cycles.<sup>22</sup> On the other hand, there are those who claim that the possible complications of bedside surgical PDA ligation outweigh the benefits, and the long-term neurodevelopmental results of the patients who have been ligated are worse. In addition, some groups try medical closure for

**Table 2.** Comparison of Pre-ligation and Post-ligation Ventilator Index (VI) Values

	Group A ( $\geq 3$ Treatment Cycle), n = 10	Group B ( $\leq 2$ Treatment Cycle), n = 14	P	
Pre-ligation VI	26.9 $\pm$ 8	19.7 $\pm$ 3.9	.007	T
Post-ligation VI 0 hours	27.8 $\pm$ 5.3	21 $\pm$ 2.7	<.001	T
Post-ligation VI 12 hours	23.4 $\pm$ 5	19.7 $\pm$ 3.4	.043	T
Post-ligation VI 24 hour	23.8 $\pm$ 5	18.9 $\pm$ 2.9	.006	T
Post-ligation VI 48 hours	23.3 $\pm$ 5.3	17.5 $\pm$ 3.6	.004	T
Post-ligation VI 72 hours	23 $\pm$ 4.9	17.4 $\pm$ 3.5	.003	T

**Table 3.** Comparison of Post-ligation Clinical Features and Morbidity Between Groups

	Group A ( $\geq 3$ Treatment Cycles), $n = 10$	Group B ( $\leq 2$ Treatment Cycles), $n = 14$	P	
Post-ligation invasive MV duration (day), median (min-max)	18 (8-43)	15.5 (7-22)	.196	U
Post-ligation non-invasive MV duration (day), median (min-max)	14.5 (5-28) *	15.5 (3-44)	.494	U
Post-ligation oxygen therapy duration (day), median (min-max)	19.5 (6-22) *	20 (9-36)	.607	U
Total (pre+post) invasive MV duration (day), median (min-max)	46 (28-79)	32 (24-44)	.004	U
Hospitalization time day, median (min-max)	100 (83-120)*	79 (56-129)	.101	U
Postconceptional week at discharge, (mean $\pm$ SD)	40 $\pm$ 2*	38.9 $\pm$ 2.2	.248	t
Discharge weight, grams, (mean $\pm$ SD)	2563 $\pm$ 493*	2543 $\pm$ 594	.937	t
BPD				$\chi^2$
Mild	0 (0)	1 (7.1)	.019	
Moderate	3 (30)	11 (78.6)		
Severe	7 (70)	2 (14.3)		
ROP				$\chi^2$
no	1 (10)	1 (7.1)		
Stage 1	1 (10)	7 (50)	.216	
Stage 2	5 (50)	3 (21.4)		
$\geq$ Stage 3	3 (30)	3 (21.4)		
PVL, $n$ (%)	1 (10)	1 (7.1)	.803	$\chi^2$
Mortality, $n$ (%)	2 (20)	0 (0)	.081	$\chi^2$

\*Group A was evaluated by excluding patients with mortality results ( $n = 8$ ).

MV, mechanical ventilation; BPD, bronchopulmonary dysplasia; ROP, retinopathy of prematurity; PVL, periventricular leucomalasia;  $\chi^2$ , chi-square test; t, independent samples t-test.

**Table 4.** Comparison of Data According to Severe BPD, which is the Main Outcome of the Study

	Severe BPD (+) ( $n = 9$ )	Severe BPD (-) ( $n = 15$ )	P	
Male Gender, $n$ (%)	5 (55)	8 (53)	.916	$\chi^2$
Need of Delivery Room Resuscitation, $n$ (%)	6 (66)	11 (73)	.728	$\chi^2$
Presence of antenatal corticosteroids, $n$ (%)	5 (55)	10 (66)	.568	$\chi^2$
Birthweight, g (mean $\pm$ SD)	940 $\pm$ 218	921 $\pm$ 179	.819	t
Gestational weeks, (mean $\pm$ SD)	27.3 $\pm$ 2.1	26.3 $\pm$ 2.9	.299	t
Surfactant dose number, median (min-max)	2 (1-4)	2 (1-3)	.897	U
Day of PDA diagnosis, (mean $\pm$ SD)	7.2 $\pm$ 2.1	6.2 $\pm$ 3.3	.416	t
Pre-ligation invasive MV duration, day, median (min-max)	31 (22-40)	17 (13-26)	.000	U
Pre-ligation sepsis, $n$ (%)	5 (55)	4 (27)	.157	$\chi^2$
Ligation day, median (min-max)	37 (24-56)	17 (13-35)	.000	U
Post-ligation invasive MV duration, median (min-max)	21 (8-43)	14 (7-21)	.045	U
Post-ligation non-invasive MV duration, day, median (min-max)	14 (5-44)*	15 (3-25)	.972	U
Post-ligation oxygen therapy duration, day, median (min-max)	20 (6-25)*	20 (9-36)	.944	U
Total invasive MV duration, day, (mean $\pm$ SD)	105 (47-129)	31 (24-45)	.000	U
PDA diameter (mm)	3.1 $\pm$ 0.6	2.7 $\pm$ 0.6	.158	t
LA/Ao ratio	1.5 $\pm$ 0.06	1.48 $\pm$ 0.08	.366	t

\*Cases resulting with mortality among patients with severe BPD were excluded ( $n = 7$ ).

BPD, bronchopulmonary dysplasia; PDA, patent ductus arteriosus; MV, mechanical ventilation; LA/Ao, left atrium aortic root ratio;  $\chi^2$ , chi-square test; t, independent samples t-test; U, Mann-Whitney U-test.



3 or 4 times considering the transport risk, because there is no pediatric cardiovascular surgery (CVS) team in their center.<sup>23</sup>

In our study, we compared 2 different approaches according to the number of pharmacologic treatment cycles in preterm infants who presented to our center for bedside PDA ligation in terms of preterm morbidities, especially BPD. We found that the rate of severe BPD was significantly higher in the group who received prolonged pharmacologic therapy.

Bronchopulmonary dysplasia is the most common chronic morbidity in preterm babies.<sup>24</sup> There is low plasma oncotic pressure and increased capillary permeability, especially in preterm babies with respiratory distress. Interstitial and alveolar edema occurs in these babies with the increase of pulmonary blood flow and microvascular pressure due to the open duct. Thus, it causes deterioration in lung mechanics and gas exchange. Increased blood flow to the immature pulmonary bed causes vascular remodeling including intimal fibrosis and medial hypertrophy, leading to increased pulmonary vascular resistance, abnormal vasoreactivity, and disruptions in alveolar development. This prolongs the duration of mechanical ventilatory support with higher pressure and oxygen concentration and increases the risk and severity of BPD. Data from the studies in preterm baboons also showed decreased alveolarization in animals that remained with an open DA for a longer time, supporting the role of a persistent PDA in the pathogenesis of BPD.<sup>25</sup> Despite this experimental and epidemiological evidence, none of the randomized clinical trials performed to date has found a relationship between therapies intended to close the PDA and the risk of developing BPD.<sup>5,16,18,26-28</sup> The reason for this is the fact that many factors other than the presence of PDA play a role in the pathogenesis of BPD and complicate the relationship between PDA and BPD.<sup>29</sup>

Several studies have shown that infants with small PDA shunts do not appear to be at increased risk for developing BPD. Instead, an association of hsPDA and BPD is apparent when moderate to large shunts persist beyond 7-14 days.<sup>30-34</sup> An infant's need for invasive respiratory support may also play an important role in determining whether prolonged PDA exposure is associated with BPD. A recent single-center study found an association between BPD and exposure to a moderate to large PDA only when infants required invasive MV for  $\geq 10$  days.<sup>34</sup> Moreover, the most recent international multicentric PDA-TOLERATE trial found that the presence of a PDA shunt was associated with an increased risk of BPD when it persisted beyond 10 days, and these infants also required prolonged intubation ( $\geq 10$  days).<sup>35</sup> In accordance with the literature, BPD developed in all subjects due to prolonged invasive MV in our study. We think that the rate of severe BPD is also higher in the prolonged medical treatment group, as the invasive MV duration is significantly longer.

The post-ligation invasive MV duration and length of hospital stay were also longer in the prolonged medical treatment group. In the ventilator index calculations for comparison of pulmonary mechanics, we have shown that the duration of invasive MV was longer and the intensity of support was higher in the group who received prolonged medical therapy, due

to long-term exposure to hsPDA. We think that this situation increases the risk of severe BPD in these subjects. As a suggestion for future prospective studies, to reduce PDA-related respiratory morbidity, the ductus can be closed earlier when the predetermined cutoff values are reached by using the ventilation index.

Bedside PDA ligation has been associated with complications such as pneumothorax, chylothorax, vocal cord paralysis, post-ligation left ventricular dysfunction, BPD, ROP, and neurodevelopmental disorder.<sup>36</sup> Although surgical mortality and morbidity are low, it is traditionally regarded as a final option for subjects unresponsive to pharmacologic treatment. In addition to this approach, medical treatment is insisted upon in some patients and the treatment may be prolonged, because the patient is not in a condition to handle the surgery, and not every center has a pediatric CVS team to perform this procedure. As a result, the patients may be exposed to hsPDA for a longer time, causing hemodynamic and respiratory disorders that may accompany a worsening condition.

When we evaluated the complications which constitute the drawbacks of bedside PDA ligation, we did not observe hemodynamic irregularity in any patient during and after the operation. We think that the reason for this is the short operation time (approximately 30 minutes) and the use of low-dose anesthesia. In addition, ventilation of premature babies during the operation by a neonatologist with neonatal-compatible ventilators might have prevented possible complications. Our study has shown once again that, in the absence of surgery-related mortality and complications, bedside surgical ligation is a safe and effective treatment and can be performed in the NICU in critically ill babies without the need for transport to the operating room. There are reports in the literature that PDA ligation may be preferred earlier, especially in preterm babies weighing less than 1000 g, because the response to medical closure treatment is lower in this patient group. In a recent meta-analysis including 6 retrospective studies involving 397 infants with very low birthweight, the early ligation group (first 2-3 postnatal weeks, differs in studies) had better respiratory outcomes compared to the late ligation group. There was no difference in mortality or postoperative complications.<sup>37</sup>

Recently, there has been an increased interest in transcutaneous closure of PDA in preterm infants, to determine whether this approach can be used as an alternative to surgical ligation or even to medical treatment, especially in the extremely low-birthweight infants. Comparison with surgical ligation revealed a positive impact on post-procedure pulmonary outcome.<sup>20,38</sup> More recently, a retrospective comparison between ligation and transcatheter closure reported prolonged MV durations and prolonged lengths of hospital stay in the ligation group.<sup>39</sup>

The limitations of our study included its retrospective nature and the fact that it included a relatively low number of subjects. Surgical PDA ligation is a rare procedure nowadays, and this was the reason why we could not perform a power analysis related to the number of patients and multivariate logistic regression analysis related to the primary outcome. Since the patients were referred from different hospitals,

there may be differences in treatments and approaches before ligation. There is a need for multicenter and well-designed prospective studies on this subject, involving a higher number of patients.

## CONCLUSION

According to our results and the literature, prolonging medical treatment in order to avoid surgery increases hospital morbidity and prolongs hospital stay. Surgical ligation could be considered in the foreground after the second unsuccessful medical treatment, in order to correct the clinical outcomes of patients. The cooperation between the neonatology, pediatric cardiology and CVS teams is very important in order to improve the clinical outcomes of these patients. Decisions about the ideal timing of surgical ligation should be made by conducting randomized prospective studies on this issue in larger populations.

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**Informed Consent:** Written informed consent was obtained from all participants who participated in this study.

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