Türk Pediatri Arşivi
Turkish Archives of Pediatrics

Turkish Neonatal Society guideline on the management of patent ductus arteriosus in preterm infants

Türk Neonatoloji Derneği prematüre bebekte patent duktus arteriozus tanı ve tedavi rehberi

Nilgün Köksal[1], Canan Aygün[2], Nurdan Uras[3]

[1]Division of Neonatology, Department of Pediatrics, Uludağ University, Faculty of Medicine, Bursa, Turkey
[2]Division of Neonatology, Department of Pediatrics, Ondokuz Mayıs University, Faculty of Medicine, Samsun, Turkey
[3]Zekai Tahir Burak Womens' Health Training and Research Hospital, Ankara, Turkey

Cite this article as: Köksal N, Aygün C, Uras N. Turkish Neonatal Society guideline on the management of patent ductus arteriosus in preterm infants. Turk Pediatri Ars 2018; 53(Suppl 1): S76-S87

Abstract

Ductus arteriosus is a physiologic phenomenon in utero and it closes spontaneously in term babies. The closure is problematic in preterm infants due to the intrinsic properties of the preterm ductus arteriosus tissue. Although patent ductus arteriosus has been reported to be associated with many adverse outcomes in this population, treatment has not led to a decrease in outcomes such as bronchopulmonary dysplasia. Treatment modalities also have their own risks and restrictions. The aim of the "Turkish Neonatal Society guidelines for the management of patent ductus arteriosus in preterm babies" is to standardize the diagnosis and treatment of patent ductus arteriosus in preterm infants by combining the current scientific data and the resources of our country.

Keywords: Diagnosis, patent ductus arteriosus, preterm, treatment

Öz

Rahim içi yaşamda fizyolojik bir gereklilik olan duktus arteriyozus term bebeklerde kendiliğinden kapanırken, prematüre duktus arteriyozus dokusunun yapısal özellikleri nedeniyle bazı prematürelerde kapanamaz. Patent duktus arteriyozus prematürelerde bronkopulmoner displazi gibi olumsuz sonuçlarla ilişkilendirildiği halde, tedavi bu olumsuz sonuçların sıklığını azaltmamıştır. Tedavinin de yan etkileri ve kullanım kısıtlılıkları vardır. Tedavi verip vermemenin ve tedavide kullanılan ajanların uzun dönem sonuçlarını bilinmemektedir. Türk Neonatoloji Derneği Prematüre Bebekte Patent Duktus Arteriyozus Tanı ve Tedavi Rehberi'nin amacı yenidoğan yoğun bakım birimlerinde izlenen prematürelerde patent duktus arteriyozus tanısı, izlemi ve tedavisi konusunda, ülkemiz koşulları ve bilimsel veriler ışığında standart bir yaklaşım sağlamaktır.

Anahtar sözcükler: Patent duktus arteriyozus, prematüre, tanı, tedavi

Introduction

Ductus arteriosus (DA), which is a physiologic necessity in in utero life, closes spontaneously in term babies, whereas the closure is problematic in preterms due to the intrinsic properties of the preterm ductus arteriosus tissue. Although patent ductus arteriosus (PDA) has been associated with many adverse outcomes in preterms, treatment has not caused a reduction in the frequency of these negative outcomes (1). Treatment modalities have their own adverse effects and restrictions. The long-term outcomes of administering or not administering treatment and the agents used in treatment are not known (2). The objective of the Turkish Neonatal Society Guideline for the Management of Patent Ductus Arteriosus in Preterm Babies is to provide a standard approach in the issue of the diagnosis, follow-up and treatment of patent ductus arteriosus in preterm babies who are being followed up in our neonatal intensive care units in view of current scientific data and the resources of our country.

1. Ductus arteriosus and physiological closure

The DA, which is a muscular artery found in all mammalian fetuses, connects the pulmonary artery (PA) to the proximal descending aorta at the intersection with the left PA. Its diameter in term babies is approximately 10 mm (until the descending aorta). In utero, the pulmonary

Corresponding Author / Sorumlu Yazar: Nilgün Köksal E-mail / E-posta: nilgunk2008@gmail.com

DOI: 10.5152/TurkPediatriArs.2018.01808

vascular resistance (PVR) is high and only 10% of the right ventricular output reaches the pulmonary circulation. Some 55-60% of the ventricular output is delivered to the systemic circulation by way of DA. The DA is kept open with the effects of prostaglandins (especially PGE1) secreted by the placenta and nitric oxide (NO) and a relatively hypoxic environment (paO_2=18-28 mm Hg) because it is a physiologic necessity in this period (3). In intrauterine life, closure of the DA spontaneously or following maternal use of non-steroidal anti-inflammatory agents results in right heart failure. After birth, VR decreases and adult pattern of circulation begins. Blood has to be delivered to the lungs; the DA is no longer required and it closes. Closure is a preprogrammed, complex process (4). It occurs in the following way:

- Increase in pO_2 with birth: As the gestational week advances, constriction in the DA, which occurs with O_2, increases. However, an increase in pO_2 is not essential in closure of the DA (for example, babies with cyanotic congenital heart disease).
- Reduction in prostaglandin (PG) level: PGs secreted from the placenta disappear. Perfusion of the lung increases, PG metabolism accelerates, and levels of PGs decrease. A sudden increase in pO_2 also decreases PG production in the DA.

Closure of the DA in term babies occurs in two steps (4):
1. Functional closure: This occurs in the 12-29th hours of life (the mean closure time is 15 hours). It is completed in 48 hours in 90% of babies and in 72 hours in the remainder. Reduction in PG levels interacts with the increase in PaO_2 synergistically. Intracellular mechanisms induced with the increase in PaO_2 cause depolarization of the cellular membrane, and entrance of calcium into the cell and contraction. Oxygen also induces secretion of endothelin-1, which is a strong vasocontrictor. Endothelin-1 increases intracellular Ca^{++} levels by way of G-proteins.

2. Anatomic (structural) closure: This is a preprogrammed remodeling process. The increase of PaO_2 in blood after birth contracts the medial smooth muscles in the DA tissue and the height of the DA shortens and thickens. This contraction obstructs the vasa vasorum and hypoxia develops in the ductal tissue. Active platelets accumulate in the DA, which is obstructed in minutes (4). Cellular death and accompanying fibrosis in the ductus permenantly closes the DA and the DA turns into the ligementum arteriosum in three weeks. Closure typically occurs from the pulmonary end towards the aortic end.

These events, which occur uneventfully in term babies, are hindered in preterm babies. The factors that are thought to be responsible for a lack closure of DA in preterm babies are as follows (4):

Table 1. Rates of spontaneous closure of the ductus arteriosus

Gestational week/ Birth weight	4th day (%)	7th day (%)	Discharge (%)
Term	100	100	100
>30 weeks	90	98	98
27- 28 weeks	22	36	–
25- 26 weeks	20	32	–
24 weeks	8	13	–
1000-1500 g	35	67	94
<1000 g	21	34	–

- The ductus arteriosus has a thin wall. The vascular wall can take O_2 by being fed directly from the lumen without a need for vaso vasorum. The necessary hypoxic environment for closure of the ductus arteriosus can not be provided (4, 5).
- Sensitivity to Ca^{++} and K^+, which increases with O_2, is low in ductal smooth muscle cells; the Ca^{++} channels are immature.
- Sensitivity to PGs (especially PGE_2) in the ductus arteriosus is high in the early gestational weeks. As gestation advances, the DA becomes more sensitive to O_2 and less sensitive to PGs.
- Prostaglandin levels: in term babies, PG levels in the circulation rapidly reduce after birth, but this reduction is slow in preterm babies because of immaturity of the lung.

2. Preterms and patent ductus arteriosus

The gestational week and birth weight influence spontaneous closure rates of PDA (Table 1). Failure of the ductus to close within 72 hours is defined as PDA. The frequency is inversely correlated with the gestational week and birth weight. The incidence of PDA is 57/100,000 live births in term babies, and is one-third in very-low-birth-weight (VLBW) babies (6, 7). The incidence of PDA in preterms is 60-70% in babies below 28 gestational weeks, 20% in babies below 32 gestational weeks; 40-55% in babies with a birth weight <1000 g, and 30% in babies with a birth weight < 1500 g. In a study conducted with 182,000 babies born before the 32nd gestational week between the years of 2003 and 2009, the incidence of PDA was found as 27% in babies who were born before the 28th week and 11% in those born between the 29th and 32nd gestational week (7). The histologic changes in the DA in term babies prevent reopening. In preterms, the DA may reopen even if it closes spontaneously or with pharmacologic treatment. The risk

of reopening defined clinically is inversely correlated with the gestational week: 37% in babies below 27 weeks, 11% in babies with a gestational age of 27-33 weeks (5).

2.1. Risk factors for patent ductus arteriosus in preterm babies

The two most important risk factors for patent DA include early gestational week and low birth weight. Perinatal asphyxia and being born at high altitude also increase the frequency of PDA. The other risk factors are as follows:

- The baby's clinical status: the frequency of PDA on the fourth day is 65% in babies born before the 30th gestational week who have received treatment because of respiratory distress syndrome (RDS) (about <28 weeks).
- Antenatal corticosteroids: Glucocorticoids are effective in the development of sensitivity especially to O_2 in the DA tissue. Spontaneous closure occurs with a lower rate in babies who have not received antenatal corticosteroids (8).
- Chorioamnionitis (CA): In a metaanalysis of 23 studies involving more than 17,000 subjects, it was found that CA increased the risk of PDA by 1.43-fold. Clinical CA is not correlated with PDA (OR: 1.28). Histologic CA (OR: 1.54) and the presence of both clinical and histologic CA (OR: 1.75) increase the risk of PDA. Antenatal steroids decrease the risk of PDA in babies with CA (OR: 0.62;) (9). In presence of chorioamnionitis, the response to cyclooxygenase inhibitors is also reduced (10).
- Phototherapy (PT): Although studies conducted in the 1970s suggested that PT caused vasodilatation by passing through the thin skin of preterms, current studies in which the diagnosis of PDA is made using echocardiography do not support the hypothesis that PT increases the frequency of PDA or elevates serum PGE_2 levels (11, 12).
- Postnatal fluid management: Studies that associated high amounts of fluid given in the first days of life with PDA were conducted in the 1970s-1980s and made the diagnosis of PDA with 'murmur.' It has been proposed that excessive fluid in VLBW babies will increase PGE_2 levels (13). Currently, it is recommended that fluid management should be conducted with close monitoring of vital signs, urine output, and biochemical results and 170 mL/kg should not be exceeded.
- Sepsis: Sepsis delays closure, decreases the response given to pharmacologic agents, and may lead to reopening of PDA.
- Intrauterine growth retardation: In the study conducted by Rakza et al. (14), the frequency of hemodynamically significant PDA (HSPDA) at the 48th hour was found as 40% in appropriate-for-gestational-age (AGA) babies and 65% in small-for-gestational-age (SGA) babies.
- Genetic factors: More than 4000 genes are expressed in the ductal tissue. In twin studies, it has been shown that genetic factors are involved in 12.6% of cases of PDA (15). Candidate genes involved in the pathogenesis of patent DA include transforming growth factor–beta, interferon (IFN) γ (+874) T allele (protective).
- Drugs: Many drugs influence PG synthesis and may contribute to the maintenance of PDA. The best known among these drugs is furosemide. Nitric oxide is a direct vasodilatator in DA; however, the frequency of PDA does not increase in babies who receive NO treatment. Nitroglycerin, nitroprussid (NO donor), and sildenafil are also vasodilatators of the DA. Although it is known that heparin and gentamycin have vasodilatator effects on the DA, there is no evidence that they increase the frequency of PDA (16).

2.2. Effect of PDA on the lungs, pulmonary circulation, and systemic circulation in preterm babies

In intrauterine life, PVR is high, systemic vascular resistance is low, and the direction of the flow in the ductus arteriosus is from right to left. After birth, PVR reduces with aeration of the lung, the systemic blood pressure (BP) becomes higher compared with the PA pressure, and the flow direction in DA reverses to left to right. In preterms, PVR is high, if RDS is present; PVR reduces after surfactant treatment and the shunt in DA reverses to left to right.

Since the diameter is small in a small PDA, there is increased resistance against the flow and left-to-right shunt is small, even if the pressure difference between the systemic and pulmonary circulation is great. If the PDA is large, the pressures in both systems are equilized and the systemic and pulmonary pressure difference determines the amount of blood in the shunt: dependent shunt. After birth, SVR does not change to a great extent and changes in PVR determine the flow in PDA. Nuclear medicine studies have shown that the amount of blood delivered from PDA to the lung may reach an amount that is three-fold the systemic blood flow (17). The delivery of blood from PDA into the lungs rather than the systemic circulation may lead hypoperfusion (ductal steal) in the end organs including the kidneys, intestines, and brain, and may cause systemic problems (18). These problems are as follows:

- If patent ductus arteriosus is large, the smooth muscle cells in the medial layer do not regress after birth because of high flow and pressure in small PAs and PVR reduces slowly and can not even return to normal levels (2).
- **Pulmonary edema:** A moderately large PDA in small

Turk Pediatri Ars 2018; 53(Suppl 1): S76-S87

preterms may lead to increased capillary permeability in both the arterial and venous ends and pulmonary edema by increasing the pulmonary venous pressure. Pulmonary edema decreases lung compliance and requirement for mechanical ventilation (MV) and O_2 increases (2, 19).

- **Pulmonary hemorrhage (PH):** PVR decreases with improvement of respiratory distress syndrome. Increased blood flow to the lung from the PDA may lead to pulmonary edema and PH. In 126 babies who were born with a gestational age below 30 weeks, it was shown that the mean PDA diameter was larger (2.0 vs. 0.5 mm) and pulmonary blood flow was higher (326 vs. 237 mL/kg/min) (19).
- **Bronchopulmonary dysplasia (BPD):** Continuous left-to-right shunt from the ductus causes fluid infiltration in the interstitium of the lung with hydrostatic pressure. Pulmonary mechanics and alveolar development are disrupted, MV time prolongs, and the risk of BPD increases (20). In preclinical studies, it has been shown that pharmacologic closure of PDA improved delay in alveolarization. However, the relation between PDA and BPD was found to be dependent on the gestational week in studies in which PDA was screened clinically and treated early (21). In a study in which prophylactic PDA ligation and post-symptom ligation were compared, prophylactic ligation was found to be an independent risk factor for BPD. The current opinion supports that both PDA and BPD develop in smaller babies (22).
- **Effect on the systemic and cerebral circulation:** When the pulmonary blood flow exceeds 50% of the systemic blood flow, a hemodynamic paradox develops as a result of immaturity of the myocardium and vascular system of the preterm. An increase in the systemic blood flow does not occur, left ventricular stroke volume increases, and heart failure develops. Diastolic regurgitation decreases brain perfusion, blood flow in the abdominal aorta decreases, the blood flow to the liver, intestines and kidneys decreases. The risk of hepatic and/or renal failure increases (16, 23).
- **Necrotizing enterocolitis (NEC):** Ductal steal increases the risk of intestinal ischemia by decreasing the SMA bood flow. Different pictures ranging from feeding intolerance to NEC are observed (16, 23).
- **Mortality:** Mortality is higher in preterms with moderately large or large PDA (2, 21).

3. Clinical signs and symptoms in PDA

Symptoms generally emerge with improvement of RDS and reduction of PVR; they are nonspecific. The clinical signs vary by the baby's weight, gestational week, and other comorbidities. The earliest signs include increased respiratory support and increased $paCO_2$ due to alveolar edema (2). Murmur is primarily heard at the 24th-72nd hour. Its severity and time period increase as the left-to-right shunt increases. It is systolic, has a high frequency, and may prolong up to diastole. It is heard at the end of the second heart sound, at the left sternal margin in the 2nd-3rd intercostal space. Continuous murmur is rare. If the shunt is large, the 3rd heart sound may be heard with rapid filling of the ventricles in diastole. The other findings include shift of the apical beat to the left side, hyperactive precordium, widening of the pulse pressure, strengthening of the peripheral pulses, signs of left ventricular failure (tachycardia, tachypnea, rales in the lung, apnea and severe bradycardia in severe cases), hepatomegaly, systolic-diastolic hypotension, and metabolic acidosis. Signs of left ventricular failure due to PDA develop earlier in preterms compared with term babies (6).

Clinical scoring systems tested for patent DA are not reliable or sensitive. The most consistent clinical finding indicating development of PDA is hypotension on the first day (especially diastolic BP <20 mm Hg) (24). Most babies in whom a large PDA was shown on echocardiography on the first four days were found to be asymptomatic. Clinical findings (especially murmur) become more distinctive after the fourth day (6). The sensitivity of the murmur is low and it is not appropriate to manage PDA only with murmur.

3.1. Terminology in PDA

Three main definitions are used in the evaluation of PDA:

- **Clinically manifested PDA:** At least one of the physical examination findings including a murmur compatible with PDA and prominent precordial beat/peripheral pulses is present. If possible, it should be proven with echocardiography because the sensitivity and specificty of the clinical findings and murmur are low (24).
- **Symptomatic PDA:** Pulmonary hyperperfusion and/or systemic hypoperfusion is present. Hypotension, difficulty in seperating the patient from MV, worsening of MV settings, persistent apnea, and PH (the most specific finding) are observed (21, 23).
- **Hemodynamically significant PDA (HSPDA):** High-volume flow in PDA is shown on echocardiography (24). Hemodynamically significant PDAs are related with PH, IVH, mortality, and severe morbidity in babies with a gestational age less than 28 weeks and closure of PDA may be considered to prevent these complications (2, 21, 23).

4. Diagnosis in patent ductus arteriosus

4.1. Chest X-ray: Enlargement in the left atrium and left

ventricle, cardiomegaly in advanced cases and clouding of the lung areas due to pulmonary congestion are observed.

4.2. Electrocardiography: ECG is not beneficial in the first stages. If a moderately large shunt continues for weeks, left ventricular hypertrophy and left atrial enlargement findings due to loading may be observed.

4.3. Echocardiography and Doppler studies: Echocardiography is the gold standard in showing PDA, the size of the shunt and its clinical significance. Structural congenital diseases should be excluded. Clinical findings are more sensitive and specific. Echocardiography makes the diagnosis of hemodynamically significant PDA 1.8 days before clinical findings (25-27). Doppler study is performed on the pulmonary artery, DA, and descending aorta. Colored Doppler gives detailed information about the shunt. Multiple parameters are evaluated because there is no single sensitive and specific parameter showing hemodynamically significant PDA. The questions to be answered and basic measurements are shown in Table 2 (2, 6, 24, 25):

Table 2. Echocardiographic principles in the diagnosis of patent ductus arteriosus

Questions to be answered	Echocardiographic measurements
Is the ductus patent?	Demonstration of PDA
If the ductus is patent, how wide is it?	Specification of the size of PDA
What is the direction of the flow in the ductus?	Demonstration of loading in the left heart and increased pulmonary circulation
What is the importance of shunt? steal How does it affect the pulmonary and systemic circulation?	Demonstration of systemic hypoperfusion due to ductal
Can the ductus close spontaneously?	

PDA: patent ductus arteriosus

Echocardiographic parameters used frequently in evaluation of hemodynamically significant PDA are as follows (Table 3) (19, 28, 29):

- Diameter of patent ductus arteriosus: if the diameter is <1.5 mm, PDA is small and does not cause marked increase in pulmonary perfusion. PDAs with a diameter of 1.5-2 mm are important (6, 19, 24, 25). The diameter of DA should be >1.4 mm/kg for HSPDA because the diameter of the ductus is also related to the baby's weight.
- Flow pattern in PDA: this gives an idea about hemodynamic status, prognosis of PDA, and management of treatment (25). These flow patterns are as follows:
  - Pulmonary hypertension pattern: This pattern is observed in the first hours of life while PVR is high. It is bidirectional: right-to-left shunt in the early systole and a small left-to-right shunt throughout the diastole.
  - Growing PDA: this shows increasing blood flow from left to right with a reduction of pulmonary vascular resistance. There is a risk for hemodynamically significant PDA.
  - Pulsatile: This is observed on the 2nd-3rd days. There is only left-to-right shunt. The shunt is pulsatile and the peak flow rate is approximately 1.5 m/s. Its sensitivity is 93.5% and specificity is 100% in HSPDA in babies weighing less than 1500 g. It is used in the treatment decision (25).
  - Closing: Continuous left-to-right flow throughout the whole cardiac cycle. The peak flow rate is higher compared with pulsatile flow because the ductus becomes narrow and the flow accelerates (2 m/s).
  - Closed: Physiologic flow is obtained in PA.

Echocardiography flow patterns in HSPDA are as follows: pulmonary hypertension-growing/ pulsatile- closing-closed; flow pattern observed in HSPDA: pulmonary hypertension- closing- closed.

- Flow in the ductus: In high volume left-to-right shunt, the end-diastolic volume is increased in the PA branches, left atrium, and left ventricle. Left ventricular output: blood delivered from the PDA to the lung is increased by 50% when the superior vena cava (SVC) flow rate is >4 (6, 19).
- Left ventricular size: Dilated left ventricle at the end of the diastole shows a large shunt.
- Left atrium:aortic root ratio (La:Ao): This is the most commonly used measurement among left cardiac measurements. The ratio of the left atrium to the aortic root is used because the left atrial size may vary by the baby's weight. It indicates marked left-to-right shunt and enlargement in the left atrium. In preterms, the LA:Ao ratio is 0.8-1.0. This ratio is >1.5 in only 5% of preterm babies who do not have PDA. If the LA:Ao ratio is >1.4, the left atrium is enlarged and HSPDA is present (6, 19, 24).
- Retrograde diastolic flow and flow rate in the descending aorta: Large PDAs causing left-to-right shunt lead to marked retrograde diastolic flow in both the thoracic and abdominal aorta, and this diastolic flow can exceed 50% of the total aortic blood flow (ductal steal) (26). When Doppler echocardiography was compared with cardiac MRI, it was found that the retrograde di-

Table 3. Echocardiographic parameters used in the evaluation of hemodynamically significant patent ductus arteriosus

Parameter	Variable	Effect of HSPDA	Threshold value
Direct evaluation of PDA			
Size	PDA diameter (mm)	Increases	Small: <1.5 mm Moderate: 1.5-2 mm Large: ≥2 mm
	PDA diameter: Left pulmonary artery diameter (on the first 4 days)	Increases	Small: <0.5 mm Moderate: 0.5- 1 mm Large: ≥1mm
	PDA diameter index (mm/ kg)	Increases	>1.4
Flow pattern	End-diastolic: peak systolic flow rate ratio in the shunt in PDA	Decreases	<0.5
Indirect markers of the shunt volume			
Increased pulmonary blood flow	Left atrium: Aortic root ratio	Increases	>15
	Left ventricular end-diastolic diameter: Aortic root ratio	Increases	>2.1
	Early and late diastolic flow ratio in the mitral valve	Increases	>1
	Left ventricular isovolumetric relaxation time (ms)	Decreases	<35
	Left ventricular output (mL/kg/min)	Increases	>314
	LPA mean antegrade flow rate (cm/s)	Increases	>42
	LPA end-diastolic antegrade flow rate (cm/s)	Increases	>20
Decreased systemic blood flow	Diastolic flow patttern in systemic arteries (descending aorta, celiac, superior mesenteric, middle cerebral)	Decreases	Small: Antegrade diastolic flow Moderate: Absence of diastolic flow Large: Retrograde diastolic flow
	Left ventricular output/ Superior vena cava flow rate	Increases	>4

HSPDA: hemodynamically significat PDA; PDA: patent ductus arteriosus; LPA: left pulmonary artery

astolic flow in the descending aorta was the echocardiographic parameter that most accurately showed high flow shunt (27).

- Transmitral passive and active flow (E and A waves): This shows diastolic filling of the left ventricle. Passive flow increases in the mitral valve because volume and pressure increase in the left atrium in patent DA. In healthy newborns, the E/A ratio is <1. In large left-to-right shunt due to patent DA, the ratio becomes >1.0. A diagnosis of PDA cannot be made with E/A ratio alone and its sensitivity decreases if patent foramen ovale is present (6).
- The end diastolic/peak systolic flow rate ratio in patent ductus arteriosus: This ratio decreases as the shunt in PDA increases.
- Myocardial flow rate and myocardial function index: This index indicates relative systolic and diastolic dysfunction. In hemodynamically significant PDA, the myocardial flow rate is reduced and myocardial function index is increased.
- PDA/left pulmonary artery (LPA) ratio: This is measured at the main PA bifurcation.
- Antegrade pulmonary artery diastolic flow rate: Under normal conditions, only systolic flow is observed in PA. Diastolic flow indicates HSPDA and increased blood flow in the lung. It is an important parameter in determining spontaneous closure (28).
- Peak systolic flow rate, end-diastolic flow rate and flow rate in the descending aorta in ductus arteriosus.

4.4. Biomarkers: Specific and sensitive biomarkers have been investigated because echocardiography is not always available and measurements on echocardiography may vary. Biomarkers can be used in three ways in PDA (30, 31):

- For making the diagnosis when the opportunity of

echocardiography is absent
- In association with echocardiography to confirm treatment decision
- In the evaluation of treatment response (Table 4).

Brain natriuretic peptide (BNP) is secreted from the ventricles as pro-BNP following pressure and volume overload. It is split into active BNP and inactive NT-proBNP in myocytes. Its half-life is 20 minutes. It causes myocardial relaxation and decreases the load of the ventricles by way of diuresis and vasodilatation when volume overload occurs in the ventricles. It inhibits renin-aldosterone production. In patent ductus arteriosus, strain in the left ventricular wall increases BNP. Screening is used to determine the size of the shunt and to evaluate treatment response. The most important reason that limits its use is overlap of BNP levels in babies who do not have PDA or who have small PDA, and in babies with moderately large/large PDA (30, 31).

In a meta-analysis that evaluated the correlation of biomarkers with echocardiographically confirmed PDA, the sensitivity and specificty were found to be 88% and 92% for brain natriuretic peptide (BNP) and 90% and 84% for NT-proBNP (31). Lack of reduction of the levels in consecutive measurements is significant. A reason for the interest in this issue is the cost of echocardiographic examination. In the United States of America, the cost of biomarkers is one-tenth of the cost of echocardiography. In our country, the work of specialist physicians is cheap and the costs of kits are high.

4.5. "Near-infrared spectroscopy" (NIRS): This method demonstrates the effects of PDA on brain blood flow.

4.6. Perfusion index (PI): Although a reduction in PI due to hemodynamically significant PDA is expected, high values may be observed after the first 24 hours because of hyperdynamic circulation. An increase in PI after the 37th hour is significant in HSPDA (32).

4.7. Platelet count: The risk of HSPDA is increased in preterms with a platelet count of 100x109 on the 1st-3rd days. However, the platelet count shows the baby's general structural maturity rather than influencing closure of DA directly and is indirectly related to PDA.

4.8. Phase contrast magnetic resonance imaging: This method shows the flow volume in the DA, thoracic artery, and veins.

5. Patent ductus arteriosus screening in preterm babies

The answer to the question as to whether echocardiographic screening should be performed in all small preterms or if one should wait until the clinical status suggests PDA, is still unclear. Screening advocates argue that the prognosis is better when PDA is screened and treated before clinical signs emerge (33-35). In a study supporting screening that involved more than 1500 babies with a gestational age under 29 weeks, the mortality (14.2% vs. 18.5%, OR: 0.73) and frequency of PH (5.7% vs. 8.4, OR: 0.6) were found to be lower in subjects in whom PDA screening with echocardiography was performed on the first three days (early) compared with those in whom screening was not performed (21). In the study conducted by Sellmer et al. (36), it was found that the presence of PDA on the third day in babies aged less than 28 weeks (especially a PDA diameter >1.5 mm) increased the mortality risk by 3.4-fold. These data support routine echocardiographic screening of VLBW babies in terms of PDA. There are no such data for larger preterm babies. When the literature information is combined with our country's conditions (lack of access to pediatric cardiologists), the recommendations related to echocardiographic PDA screening are as follows:

- In babies less than 28 weeks and/or <1000 g: in the first 72 hours;
- In high-risk babies less than 28 weeks and/or <1000 g who are being monitored with MV because of RDS: in the first 24-72 hours because of the positive effect of early diagnosis and treatment of PDA on PH and mortality;
- In babies over 28 weeks and/or >1000 g connected to a ventilator: echocardiographic examination is recommeded when the clinical and respiratory findings suggest ductal shunt.

Table 4. Biomarkers used in the diagnosis of patent ductus arteriosus (30, 31)

Biomarker	Sample	Relation with PDA
Atrial natriuretic peptide	Blood and urine	Increases
Cardiac Troponin-T	Blood	Increases
Brain natriuretic peptide	Blood and urine	Increases
Amino-terminal pro-B-tip natriuretic peptide (NTproBNP)	Blood and urine	Increases
Endothelin-1 and C-terminal pro-endothelin-1	Blood and urine	Increases
Neutrophil gelatinase-associated lipocalin	Urine	Increases
Cardiac fatty acid binding protein	Urine	Increases in HSPDA

HSPDA: hemodynamically significant PDA; PDA: patent ductus arteriosus

Turk Pediatri Ars 2018; 53(Suppl 1): S76-S87

6. Treatment of patent ductus arteriosus in preterm babies

There are three up-to-date approaches: Conservative treatment, cyclooxygenase (COX) inhibitors and surgical treatment.

6. 1. Conservative treatment

- Neutral thermal environment and sufficient oxygenation: decreases left ventricular load
- The hematocrit level should be kept between 35% and 40%.
- Increased positive expiration pressure (PEEP>5) and short inspiration time (0.35 s): gas exhange improves, left-to-right shunt decreases, and systemic blood flow increases.
- Diuretics: Thiazide group diuretics are used in cases of pulmonary edema and increased MV support. Loop diuretics are not recommended because they increase renal PGE_2 synthesis and keep the DA open (36).
- Fluid restriction: Fluid should be restricted if pulmonary edema due to HSPDA and severe respiratory distress are present: 110-130 mL/kg/day. According to Cochrane, fluid restriction (50-80 mL/kg/day) reduces the risk of PDA and NEC when compared with liberal (80-170 mL/kg/day) administration of fluid (NNT:7) (37). If fluid intake is >170 mL/kg on the third day, this is an independent risk factor for symptomatic PDA. It should be kept in mind that severe fluid restriction will negatively influence nutrition and growth of the preterm baby.
- Feeding: A negative effect of feeding during symptomatic PDA and treatment has not been demonstrated (38). Feeding should be continued carefully.

6.2. Pharmacologic treatment: Indomethacin and ibuprofen inhibit COX 1 and 2, decrease PG synthesis, and induce closure of DA (39). There are three approaches: prophylactic, asymptomatic, and symptomatic treatment.

6.2. a. Prophylactic treatment: Administration of treatment in the first 12-24 hours of life before PDA symptoms develop in high-risk group patients. The objective is to prevent intracranial hemorrhage (ICH) and PDA.

- Prophylactic indomethacin: Meta-analyses have shown a 50% reduction in HSPDA, a 35% reduction in ICH (>stage 2) and a 50% reduction in need for surgical ligation (SL). However, this approach has no effect on mortality, BPD, and neurodevelopmental prognosis in the 18^{th} to the 36^{th} months (40).
- Prophylactic ibuprofen: This can be administered orally or by the intravenous route. In a meta-analysis, it was reported that prophylactic ibuprofen decreased PDA and the need for SL, but was not beneficial in terms of BPD, mortality, and ICH (41).

Currently, prophylactic treatment is not recommended because preterms who do not have HSPDA are also exposed to potential adverse effects of drugs and because it has no positive effect on long-term neurodevelopmental prognosis or on the rate of survival without sequela, despite its advantages.

6.2.b. Early asymptomatic treatment: Administration of treatment with echocardiographic screening before symptoms develop. It has no effect on the rate of mortality, retinopathy of prematurity (ROP), NEC or BPD. However, it slightly decreases the frequency of symptomatic PDA, additional oxygen time, and the frequency of PH in extremely-low-birth weight (ELBW) babies (42).

6.2.c. Early symptomatic (2-5 days) and late symptomatic (10-14 days) treatment: The first studies comparing these two treatments supported early symptomatic treatment because it decreased the MV period and the frequency of BPD. Currently, short-term intubation and non-invasive ventilation applications have changed. Therefore, the advantages and disadvantages of these two approaches should be compared again.

6.3 Drugs used in the treatment of patent ductus arteriosus

- **Indomethacin:** In a multi-center study comparing indomethacin and placebo (3559 babies, 421 of whom had HSDA), the rate of functional closure in the first 48 hours was found to be higher in the indomethacin group (79% vs. 28%). Reopening was observed in 33% of the patients and most of these patients did not need treatment (43). The potential adverse effects include transient renal disorder, gastrointestinal (GI) hemorrhage, and focal GI perforation. In a Cochrane meta-analysis, it was reported that the infusion time of indomethacin did not influence the rate of closure/reopening of PDA, neonatal mortality, and the frequency of ICH and NEC. DA is not closed with indomethacin in one-third of patients. The rate of ductal closure is 42% with a second course of indomethacin and 43% with a third course of indomethacin. Cumulative closure reaches 90% with three courses, but the risk of periventricular leukomalacia (PVL) increases (44). If DA is not closed after the second indomethacin dose, SL is considered.
- **Ibuprofen:** Ibuprofen is the second most commonly used COX inhibitor in the treatment of PDA. Its efficiency in closing PDA is equal to the efficiency of

Table 5. Drugs used in treatment of patent ductus arteriosus and their doses

Drug	Dose (mg/kg)	Route of administration	Rate of closure of PDA (%)	Adverse effects	Reopening (%)
Indomethacin	<48 hours	IV At least 30 min	70-80	Oliguria, reduction in creatinine clearance, electrolyte imbalance, bleeding in GIS, NEC, perforation	20-35
	1st dose: 0.2 mg/ kg 12 hours later 2nd dose: 0.1 mg/kg 24 hours later 3rd dose: 0.1 mg/kg				
	>48 hours 0.2 mg/kg with 12-24-hour intervals				
Ibuprofen	Loading: 10 mg/kg with 24-hour intervals 5 mg/kg, 2 successive doses	IV or oral	70-80	Oliguria, reduction in creatinine clearance, hyperbilirubinemia, bleeding	30
Paracetamol	15 mg/kg every 6 hours, po	Oral or IV 2-7 days	90- 100	Increase in liver enzymes	30

GIS: gastrointestinal system, PDA: patent ductus arteriosus, NEC: necrotizing enterocolitis

indomethacin. The risks of necrotizing enterocolitis and renal adverse effects are lower and the MV time is shorter; the frequency of PH is similar to indomethacin. In developed countries, it is administered intravenously (44). However, oral ibuprofen is preferred in many developing countries because intravenous preparation is expensive and no difference has been found in PDA closure rates. Oral ibuprofen and intravenous indomethacin are similar in terms of closing PDAs and adverse effects. There are new studies that have shown that both intravenous and high-dose oral ibuprofen (20-10- 10 mg/kg) are more efficient in PDA treatment in younger gestational weeks (43-45). In a pharmacokinetic study, ibuprofen doses recommended for PDA treatment were as follows: <70th hour: 10-5- 5 mg/kg; 70th-108th hours: 14 - 7 - 7 mg/kg; 108th-180th hours: 18 - 9 - 9 mg/kg (45). High-dose ibuprofen treatment is recommended after the 70th hour because renal clearance increases. If PDA is not closed after the first standard dose course, it is preferred as a second course. In a new study, administration of high-dose ibuprofen in the first course was reported to be more efficient and similar in terms of adverse effects (46) (Table 5).

Contraindications of cyclooxygenase inhibitors: confirmed or suspected sepsis, NEC, active bleeding (intracranial, GI), thrombocytopenia (<50,000/ mm^3), coagulation disorder, renal failure (urine output <0.6 mL/kg/ hour, creatinine >1.6 mg/dL), GI or renal anomaly, DA-dependent congenital heart disease. Ibuprofen and indomethacin increase the risk of kernicterus by competing with bilirubin for albumin binding sites (more prominent with ibuprofen). Enteral nutrition is safe during COX inhibitor treatment (38).

- **Paracetamol:** Paracetamol inhibits the peroxidase (POX) component of prostaglandin synthesis. It was primarily used in babies who were unresponsive to treatment or in those in whom COX inhibitors were contraindicated and the rate of closure of DA was observed to be above 90%. In a study conducted in our country that compared oral paracetamol with oral ibuprofen, the rates of ductal closure, reopening, and SL were found to be similar and no difference was found in terms of adverse effects (47). The dose used is higher than the dose recommended for pain and fever and there are concerns about hepatotoxicity. In animal studies, it has been reported that paracetamol has negative effects on the developing brain and prenatal exposure is associated with childhood autism spectrum disorders. Therefore, paracetamol is not the standard treatment option; studies need to be conducted to demonstrate its efficiency and safety. Table 6 shows the drugs used in the treatment of PDA and their doses.

Table 6. The Turkish Neonatal Society evidence-based recommendations for approaching patent ductus arteriosus of prematurity

Hemodynamically significant PDA- Diagnosis	
1. Echocardiography	Targeted neonatal echocardiography and presence of clinical finding
	Ductal diameter ≥1.4mm/kg, La:Ao>1.4
	Direction of the ductal shunt and flow rate
	Pulse Doppler flow pattern
	Other findings of the ductal shunt flow
2. Biomarkers	NtP-pBNP >1000, after the first 48 hours
	Treatment decision: Monitoring with clinical and ECHO findings: repeated measurements
Hemodynamically significant PDA – Treatment	
Fluid restriction	First 72 hours: 110-130 mL/kg at most, subsequent days: 170 mL/kg at most
Supportive treatment	Appropriate neutral environment, diuretic: Furosemid should be avoided
Pharmacologic treatment	
Ibuprofen	First-line choice
	First 48 hours: intravenous treatment, after 48 hours: oral treatment (as efficient as intravenous treatment)
Indomethacin	Prophylactic treatment is not recommended
	Continuous infusion is preferred rather than bolus infusion
	Repeated, if necessary (2 doses at most, PVL risk with excessive doses)
Paracetamol	Routine use is not recommended. Long-term safety?
	Intravenous route, if ibuprofen or indomethacin treatment is contraindicated
Surgical approach	Prophylactic surgery is not recommended
	If HSPDA is not closed after two courses of pharmacotherapy
Interventional approach	VATS is less invasive compared to surgical ligation
	Transcatheter application is not recommended for all patients

ECHO: echocardiography; HSPDA: hemodynamically significant PDA; PDA: patent ductus arteriosus; PVL: periventricular leukomalacia; VATS: video-assisted thoracoscopic surgery

The recommendation of the Turkish Neonatal Society: Patients who do not respond to the first course of medical treatment generally do not respond to successive courses either. If HSPDA is present after the first course, the second ibuprofen course can be given with normal or high dose. If no response is obtained, paracetamol may be tried before SL. Studies need to be conducted to show the efficiency and long-term safety of paracetamol before it becomes a routine recommendation.

6.4. Surgical treatment

PDA of prematurity closes with SL with a rate of 98-100% (7, 48). Severe hypotension (25%), unilateral cord paralysis, and scoliosis may be observed postoperatively. Currently, video-assisted thoracoscopic surgery (VATS) is applied instead of posterolateral thoracotomy in many centers. Although the results are similar, VATS is less invasive. Extremity ischemia and catheter malposition may be observed in preterms following PDA closure using the transcatheter method, which is applied in term babies. Promising studies have been conducted with ADO II AS devices in smaller babies (49).

The recommendation of the Turkish Neonatal Society: SL should be considered in babies in whom respiratory support continues or in babies with HSPDA on echocardiography who do not respond to medical treatment (generally after the 2nd course) or who are found to have contraindications.

Conclusion

Early and prophylactic treatment decreases the rate of PVL/IVH and PH and successive pharmacologic treatment decreases the need for SL. However, a positive effect on the prognosis could not be demonstrated in surviving babies and it has not been widely accepted. The greatest benefit and the lowest risk can be provided if early prophylactic treatment is targeted only for preterms

with insufficient ductal constriction. In recent years, an early targeted individual approach by echocardiography has been recommended in preterms with a gestational age less than 29 weeks (19, 21, 24). The 2016 report of the American Academy of Pediatrics states that prophylactic indomethacin/ibuprofen can be given to high-risk babies (<29 weeks) if a center has high rates of ICH and/or severe PH (50).

In babies with a gestational age under 28 weeks or with a birth weight below 1000 g, echocardiographic examination in the first 72 hours is generally recommended for PDA screening. In high-risk babies who are connected to a ventilator because of RDS with a gestational age less than 28 weeks and a birth weight below 1 000 g, early diagnosis and treatment of PDA may have a positive effect especially on pulmonary hemorrhage and mortality. Therefore, echocardiographic examination in the first 24-72 hours is an option in terms of early treatment of hemodynamically significant PDA in high-risk babies who are connected to a ventilator because of RDS. In babies with a gestational age above 28 weeks and/or with a birth weight over 1000 g who are connected to a ventilator, echocardiographic examination is recommended if clinical and respiratory findings suggest ductal shunt. Treatment is initiated if clinical and ECHO findings support hemodynamically significant PDA.

In our country, the first-line agent for treatment is ibuprofen. Ibuprofen is used at a dose of 10 mg/kg-5 mg/kg-5mg/kg in three doses. Ibuprofen is used intravenously in the first 48 hours. Oral treatment should be used if symptomatic PDA is to be treated after the 48th hour and if the baby can tolerate feeding. Ideally, echocardiography should be repeated before the second dose of medical treatment. There is evidence showing that successive doses are not needed if the ductal diameter is <1.5 mm. In babies with PDA in whom clinical findings continue after two courses of pharmacotherapy, surgical treatment should be considered. Prophylactic surgical treatment is not recommended.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study has received no financial support.

Çıkar Çatısması: Yazarlar çıkar çatışması bildirmemişlerdir.

Mali Destek: Yazarlar bu çalışma için mali destek almadıklarını beyan etmişlerdir.

References

1. Evans N. Preterm patent ductus arteriosus: A continuing conundrum for the neonatologist. Semin Fetal Neonatal Med. 2015;20:272-7. [CrossRef]
2. Philips JB, Garcia-Pratz JA, Fulton DR, Kim MS. http://www.uptodate.com/contents/. Management of patent ductus arteriosus in preterm infants.
3. Hamrick SE, Hansmann G. Patent ductus arteriosus of the preterm infant. Pediatrics 2010;125:1020-30. [CrossRef]
4. Coceani F, Baragatti B. Mechanisms for ductus arteriosus closure. Semin Perinatol 2012; 36:92-97. [CrossRef]
5. Weiss H, Cooper B, Brook M, et al. Factors determining reopening of the ductus arteriosus after successful clinical closure with indomethacin. J Pediatr 1995; 127:466-471. [CrossRef]
6. Moore P, Brook MM. Patent Ductus Arteriosus and aorticopulmonary window. İç: Moss and Adams' Heart Disease. Allen HD, Driscoll DJ, Shaddy RE, Feltes TF (eds). Wolters Kluwer- Lipincott Williams& Wilkins, Philadelphia, ABD, 8. baskı, 2013, pp. 722- 745.
7. Weinberg JG,Evans FJ,Burns KM,Pearson GD,Kaltman JR. Surgical ligation of patent ductus arteriosus in premature infants: trends and practice variation. Cardiol Young 2015 23:1-8.
8. Clyman RI, Ballard PL, Sniderman S. Prenatal administration of betamethasone for prevention of patient ductus arteriosus. J Pediatr 1981;98:123–126. [CrossRef]
9. Park HW1, Choi YS2, Kim KS1, Kim SN. Chorioamnionitis and patent ductus arteriosus: A systematic review and meta-analysis. PLoS One. 2015;16;10:e0138114.
10. Kim ES, Kim EK, Choi CW, Kim HS, Kim BI, Choi JH. Intrauterine inflammation as a risk factor for persistent ductus arteriosus patency after cyclooxygenase inhibition in extremely low birth weight infants. J Pediatr 2010; 157: 745–750 e741.
11. Barefield ES1, Dwyer MD, Cassady G. Association of patent ductus arteriosus and phototherapy in infants weighing less than 1000 grams. J Perinatol. 1993;13:376-80.
12. Surmeli-Onay O, Yurdakok M, Karagoz T, et al. A new approach to an old hypothesis; phototherapy does not affect ductal patency via PGE_2 and PGI2. Matern Fetal Neonatal Med 2015;28:16-22. [CrossRef]
13. Stonestreet BS, Bell EF, Warburton D, Oh W.Am J Dis Child 1983;137:215-9. [CrossRef]
14. Rakza T, Magnenant E, Klosowski S, Tourneux P, Bachiri A, Storme L. Early hemodynamic consequences of patent ductus arteriosus in preterm infants with intrauterine growth restriction. J Pediatr 2007; 151: 424- 428. [CrossRef]
15. Bhandari V, Zhou G, Bizzarro MJ, et al. Genetic contribution to patent ductus arteriosus in the premature newborn. Pediatrics 2009; 123: 669–673. [CrossRef]
16. Capozzi G1, Santoro G. Patent ductus arteriosus: pathophysiology, hemodynamic effects and clinical complications. J Matern Fetal Neonatal Med. 2011;24 Suppl 1:15-6
17. Vick GW 3rd, Satterwhite C, Cassady G, et al. Radionuclide angiography in the evaluation of ductal shunts in preterm infants. J Pediatr 1982; 101:264. [CrossRef]
18. Jain A, Shah PS. Diagnosis, evaluation, and management of patent ductus arteriosus in preterm neonates. JAMA Pediatr 2015;169:863-72. [CrossRef]

19. Kluckow M, Evans N. Ductal shunting, high pulmonary blood flow, and pulmonary hemorrhage. J Pediatr 2000; 137:68. [CrossRef]
20. Marshall DD1, Kotelchuck M, Young TE, Bose CL, Kruyer L, O'Shea TM. Risk factors for chronic lung disease in the surfactant era: a North Carolina population-based study of very low birth weight infants. Pediatrics 1999;104:1345-50
21. Rozé JC, Cambonie G, Marchand-Martin L, & Hemodynamic EPIPAGE 2 Study Group. Association between early screening for Patent Ductus Arteriosus and in-hospital mortality among extremely preterm infants. JAMA. 2015;313:2441-2448. [CrossRef]
22. Chock VY, Punn R, Oza A, et al. Predictors of bronchopulmonary dysplasia or death in premature infants with a patent ductus arteriosus. Pediatr Res 2014 ;75:570-575.
23. Evans N, Moorcraft J. Effect of patency of the ductus arteriosus on blood pressure in very preterm infants. Arch Dis Child. 1992;67(10, spec no):1169-1173.
24. Writing group of American Society of Echocardiography in collaboration with the European Association of Echocardiography and the Association for European Pediatric Cardiologists. Targeted neonatal echocardiography in the neonatal intensive care unit: practice guidelines and recommendations for training. Eur J Echocardiography 2011; 12, 715–736. [CrossRef]
25. Su BH, Watanabe T, Shimizu M, Yanagisawa M. Echocardiographic assessment of patent ductus arteriosus shunt flow pattern in premature infants. Arch Dis Child 1997;77: F36–F40. [CrossRef]
26. Groves AM, Kuschel CA, Knight DB, Skinner JR. Does retrograde diastolic flow in the descending aorta signify impaired systemic perfusion in preterm infants? Pediatr Res 2008;63:89-94. [CrossRef]
27. Broadhouse KM, Price AN, Druigel H, Cox AJ, Finnemore AE. Assessment of PDA shunt and systemic blood flow in newborns using cardiac MRI. NMR Biomed 2013;26:1135-41. [CrossRef]
28. Weiss DM, Kaiser JR, Swearingen C, Malik S, Sachdeva R. Association of antegrade pulmonary artery diastolic velocity with spontaneous closure of the patent ductus arteriosus in extremely low-birth-weight infants. Am J Perinatol 2015; 32: 1217- 1224. [CrossRef]
29. Zonnenberg I, de Waal K. The definition of a haemodynamic significant duct in randomized controlled trials: a systematic literature review. Acta Paediatr 2012;101:247-251.
30. Evans N. Diagnosis of the preterm patent ductus arteriosus: Clinical signs, biomarkers, or ultrasound? Semin Perinatol 2012;36:114-122. [CrossRef]
31. Kulkarni M, Gokulakrishnan G, Price J, et al. Diagnosing significant PDA using natriuretic peptides in preterm neonates: a systematic review. Pediatrics 2015;135:e510-e525 [CrossRef]
32. Alderliesten T, Lemmers PM, Baerts W, Groenendaal F, van Bel F. Perfusion index in preterm infants during the first 3 days of life. Neonatology 2015;107:258-65. [CrossRef]
33. Kluckow M, Jeffery M, Gill A, Evans N. A randomised placebo-controlled trial of early treatment of the patent ductus arteriosus. Arch Dis Child Fetal Neonatal Ed 2014; 99:F99. [CrossRef]
34. Rajadura VS. Current controversies in the management of patent ductus arteriosus in preterm infants. Indian Pediatr 2014; 51: 289- 294. [CrossRef]
35. Ibrahım TK, Abdulhaum AA, Chandran Souvik M, et al. Management of patent ductus arteriosus in preterm infants- Where do we stand? Congenit Heart Dis 2013; 8: 500- 512. [CrossRef]
36. Sellmer A, Bjerre JV, Schmidt MR, et al. Morbidity and mortality in preterm neonates with patent ductus arteriosus on day 3. Arch Dis Child Fetal Neonatal Ed. 2013;98:F505-F510. [CrossRef]
37. Bell EF, Acaregui MJ. Restricted versus liberal water intake for preventing morbidity and mortality in preterm infants. Cochrane Database Syst Rev. 2008;1:CD000503
38. Clyman R, Wickremasinghe A, Jhaveri N, et al. Enteral feeding during indomethacin and ibuprofen treatment of patent ductus arteriosus. J Pediatr. 2013;163:406–11.
39. Knight DB. The treatment of patent ductus arteriosus in preterm infants: a review and overview of randomized trials. Semin Neonatol 2001; 6 (1): 63-73 46.
40. Schmidt B, Davis P, Moddemann D, et al. Long- term effects of indomethacin prophylaxis in extremely low birth weight infants. N Engl J Med. 2001;344:1966–72. [CrossRef]
41. Ohlsson A, Walla R, Shah SS. İbuprofen for the treatment of patent ductus arteriosus in preterm or low birth weight (or both) infants. Cochrane Database Syst Rev 2015;18: CD003481. [CrossRef]
42. Kluckow MR, Jeffery M, Gill A, Evans N. A randomised placebo controlled trial of early treatment of the patent ductus arteriosus. Arch Dis Child 2014; F99- F104. [CrossRef]
43. Fowlie PW, Davis PG, McGuire W. Prophylactic intravenous indomethacin for preventing mortality and morbidity in preterm infants. Cochrane Database Syst Rev CD000174, 2010. [CrossRef]
44. Gokmen T, Erdeve O, AltugN, Oguz SS, Uras N, Dilmen U. Efficacy and safety of oral versus intravenous ibuprofen in very low birth weight preterm infants with patent ductus arteriosus. J Pediatr. 2011;158:549–554. [CrossRef]
45. Hirt D, Van Overmeire B, Treluyer J-M, et al. An optimized ibuprofen dosing scheme for preterm neonates with patent ductus arteriosus, based on a population pharmacokinetic and pharmacodynamic study. Br J Clin Pharmacol 2008;65:629–636. [CrossRef]
46. Dani C, Vangi V, Bertini G, et al. High-dose ibuprofen for patent ductus arteriosus in extremely preterm infants. Clin Pharmacol Ther 2012;91:590–596. [CrossRef]
47. Oncel MY, Yurttutan S, Erdeve O, Uras N, et al. Oral paracetamol versus oral ibuprofen in the management of patent ductus arteriosus in preterm infants: a randomized controlled trial. J Pediatr 2014;164:510-4.e1. [CrossRef]
48. Mosalli R, Alfaleh K. Prophylactic surgical ligation of patent ductus arteriosus for prevention of mortality and morbidity in extremely low birth weight infants. Cochrane Database Syst Rev 2008; (1): CD00618160. [CrossRef]
49. Kenny D, Morgan GJ, Bentham JR, et al. Early clinical experience with a modified amplatzer ductal occluder for transcatheter arterial duct occlusion in infants and small children. Catheter Cardiovasc Interv 2013; 82: 534- 540.
50. Benitz WE, Committee on fetus and newborn. Patent Ductus Arteriosus in Preterm Infants Pediatrics 2016;137:1-6.