



Which Criteria are More Valuable in Defining Hemodynamic Significance of Patent Ductus Arteriosus in Premature Infants? Respiratory or Echocardiographic?

Prematüre Bebeklerde Hemodinamik Anlamlı Patent Duktus Arteriyozusun Tanımlanmasında Hangi Kriterler Daha İyidir? Solunumsal mı Ekokardiyografik mi?

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Abstract

Aim: Patent ductus arteriosus (PDA) is a frequent health problem in premature infants. Pharmacologic closure is recommended only for hemodynamically significant PDA (hsPDA) that is defined according to the clinical and echocardiographic criteria. The aim of this study was to explore the value of commonly used criteria in defining hsPDA and predicting the required number of courses of ibuprofen treatment to close PDA in premature infants.

Methods: Sixty premature infants with a gestational age of ≤ 33 weeks were evaluated prospectively. Clinical and echocardiographic criteria [O_2 requirement, ductus diameter (DD) and left atrial-to-aortic root diameter ratio (LA:Ao)] were used to define hsPDA. Clinical improvement after pharmacologic closure of PDA and association between the criteria and required number of ibuprofen courses were investigated.

Results: O_2 requirement decreased by PDA closure but was not different between patients with hsPDA and the others with PDA. Also, O_2 requirement was not found to be associated with required number of ibuprofen courses. DD and LA:Ao were greater in patients with hsPDA. DD was found to be associated with required number of courses of ibuprofen treatment.

Conclusion: Although there was an improvement in O_2 requirement with PDA closure, echocardiographic criteria were found to be more valuable in defining hsPDA. DD should also be used to estimate the duration of treatment.

Keywords: Criteria, patent ductus arteriosus, prematurity

Öz

Giriş: Patent duktus arteriyozus (PDA) prematüre bebeklerde sık karşılaşılan bir problemdir. Farmakolojik kapama sadece klinik ve ekokardiyografik kriterlerle tanımlanan hemodinamik anlamlı PDA (haPDA) için önerilmektedir. Bu çalışmanın amacı yaygın olarak kullanılan kriterlerin haPDA tanımlanmasındaki ve PDA kapatılması için gereken ibuprofen kür sayısını tahmin etmedeki değerini incelemektir.

Yöntemler: Gestasyonel yaşı ≤ 33 hafta olan 60 prematüre bebek prospektif olarak incelenmiştir. Klinik ve ekokardiyografik kriterler [O_2 ihtiyacı, duktus çapı (DÇ) ve sol atriyumun aort köküne oranı (SA:Ao)] haPDA tanımlanmasında kullanıldı. PDA'nın farmakolojik kapatılmasından sonra klinik düzelme olması ve kriterler ile gereken ibuprofen kür sayıları arasındaki ilişki incelendi.

Bulgular: O_2 ihtiyacı PDA kapanması ile azalmakla birlikte bu azalma haPDA olan bebeklerde diğer PDA olan bebeklerden farklı değildi. Ayrıca O_2 ihtiyacı ile gereken ibuprofen kür sayısı arasında ilişki bulunmadı. DÇ ve SA:Ao haPDA olan bebeklerde daha büyüktü. DÇ gereken ibuprofen kür sayısı ile ilişkili bulundu.

Sonuç: PDA kapanması ile O_2 ihtiyacında düzelme görülmeyle birlikte ekokardiyografik kriterler haPDA tanımlanmasında daha değerli bulunmuştur. DÇ ayrıca tedavi süresini tahmin etmede kullanılabilir.

Anahtar Sözcükler: Kriterler, patent duktus arteriyozus, prematürite

Introduction

Ductus arteriosus (DA) is the arterial structure between the pulmonary artery and aorta and normally closes spontaneously after birth (1). Patent ductus arteriosus (PDA) is a congenital abnormality in which DA remains open and it is a frequent problem in neonatology units, especially among preterm infants (2). The incidence of PDA is inversely proportional to gestational age (GA) (3). PDA occurs in about one-third of preterm infants, two-thirds of extremely low-birth-weight infants and 75% of those born before 28 weeks of gestation (4-6).

Hemodynamically significant PDA (hsPDA) can result in congestive heart failure, pulmonary edema-bleeding, bronchopulmonary dysplasia, intraventricular hemorrhage, necrotizing enterocolitis, feeding intolerance, and retinopathy in premature infants (7).

The safety and efficacy of closing PDA by pharmacologic agents and surgery are well defined. However, there is not a complete consensus on patient selection and optimal method and timing for closing PDA in premature infants. Also, long-term benefits of closing PDA are still controversial (8). Therefore, PDA treatment strategies differ between centers. The decision whether, when, or how to administer therapies to close PDA in premature infants remains challenging (9). Treatment is commonly prescribed for hsPDA (10).

Most centers use clinical criteria [(a) respiratory signs, including increased respiratory support, failure to wean from respiratory support or O₂ need; (b) physical signs, including murmurs, hyperdynamic precordium or bounding pulses; (c) blood pressure problems, including decreased mean or diastolic pressure or increased pulse pressure; (d) signs of congestive heart failure, including cardiomegaly, hepatomegaly or pulmonary congestion] and echocardiographic criteria [(a) a left atrial-to-aortic root diameter ratio of >1.30 (LA:Ao); (b) a ductus diameter (DD) of >1.5-2 mm] to define hsPDA but there is a wide variety of strategies used in different clinics (10).

In this study, we aimed to investigate the value of commonly used clinic (O₂ requirement) and echocardiographic (DD, LA:Ao) criteria in defining hsPDA and in predicting the required number of courses of ibuprofen treatment to close PDA in premature infants.

Methods

This prospective study was performed in the neonatology department at Atatürk University Faculty of Medicine between October 2011 and April 2013. The study was approved by the local ethics committee. Premature infants with a GA of ≤33 weeks who had hsPDA or insignificant PDA (hiPDA) were included in the study.

Clinical and echocardiographic evaluations were performed to define hsPDA in cooperation with neonatology and pediatric cardiology physicians. We used respiratory problems (respiratory distress, increased O₂ or ventilation requirements, tachypnea, hypoxia, and apnea without an evident reason) as clinical criteria and large ductal size (>1.5 mm) and increased LA:Ao (>1.4) as echocardiographic criteria. M-mode images of the left atrium and aortic root were obtained from a parasternal long-axis view. Ductal sizes were obtained by both B-mode and color Doppler from the high left parasternal view but predominantly the narrowest diameter of color Doppler flow in parasternal short axis view was used to determine the ductal diameter because it is hard to achieve reliable anatomic measurements with B-mode.

Premature infants with hiPDA were followed up only with conservative approaches. In the absence of contraindications, enteral ibuprofen was used to close hsPDA in 60 premature infants.

Enteral ibuprofen was administered via nasogastric tube as courses. Three doses (10, 5 and 5 mg/kg) were accepted as one course and the treatment protocol consisted of up to 3 courses (9 doses). Echocardiographic evaluations were performed after courses. In case of hsPDA continuation after 3 courses, patients were referred for surgical closure.

GA, mechanical ventilation parameters, DD, and LA:Ao were recorded during treatment. Echocardiographic investigations were performed by the same physician with a Vivid 7 echocardiography device (General Electric, USA®) and 10S probe.

Statistical Analysis

Descriptive methods (frequency, percentage, mean, standard deviation) were used to analyze data and the Kolmogorov-Smirnov test to analyze normality of distribution. Pearson's chi-square test and Fisher's exact tests were used for comparison of qualitative data. The independent samples t-test was used for quantitative comparison of data between two groups. One-way ANOVA was used for comparison of data between groups more than two. The results were analyzed at a 95% confidence interval and a p value of less than 0.05 was considered statistically significant.

Results

53.3% (32/60) and 48.4% (30/62) of subjects were female and 46.7% (28/60) and 51.4% (32/62) were male in hsPDA and hiPDA groups, respectively (p=0.076). The mean GA was 29.18 and 29.76 weeks in hsPDA and hiPDA groups, respectively (p=0.125). In two patients, ibuprofen was contraindicated due to necrotizing enterocolitis (one had thrombocytopenia also). In these

patients, successful pharmacologic closure was achieved with paracetamol. Oxygen need was not significantly different between premature infants with hiPDA and hsPDA before PDA closure (Table 1). However, there was a significant difference in O₂ requirement of patients after PDA was closed pharmacologically (Table 2). Two patients underwent surgical closure after 3 courses of ibuprofen failed and these patients were not evaluated in terms of oxygen need. DD and LA:Ao were found to be significantly greater in patients with hsPDA and hiPDA (Table 3). There was no significant relationship between the required number of ibuprofen courses to close PDA and O₂ requirement or LA:Ao in patients but DD was found to be significantly higher in patients who required 2 and 3 courses than in those required 1 (Table 4).

Discussion

The relationship of PDA and associated morbidities with utility of closing PDA pharmacologically is subject of discussion and closing PDA pharmacologically is not a standard recommendation for premature infants. Clinicians should weigh the risks associated with medications to close

PDA versus PDA. The decision of pharmacologic treatment should be based on hemodynamic significance of PDA but this is not always easy to identify (3,11). Many criteria have been used to define hsPDA in premature infants.

In recent publications, it has been shown that electrocardiographic and radiological criteria were nonspecific. Clinical (respiratory signs, physical signs, blood pressure problems, congestive heart failure signs) and echocardiographic (LA:Ao>1.30 and DD>1.5-2 mm) criteria were commonly used to define hsPDAs (10). Unfortunately, the optimal criteria for defining hsPDA are lacking and there is a wide variety of strategies used in different clinics (12). Therefore, the optimal timing of pharmacological treatment for PDA in preterm infants is still controversial (13).

In a study, 29.5%, 16.7% and 53.8% of patients with hsPDA were found to be on O₂ supplement, continuous positive airway pressure and synchronized intermittent mandatory ventilation (1). In our study, O₂ requirements were not found to be different between patients with hiPDA and hsPDA (Table 1). This suggests that O₂ need was not a good criterion for defining hsPDA.

Some studies reported positive changes in lung compliance in premature infants (14,15) but some

Table 1. O₂ requirements in patients with hemodynamically insignificant patent ductus arteriosus and hemodynamically significant patent ductus arteriosus before patent ductus arteriosus closure

	hiPDA		hsPDA	
	n	%	n	%
O ₂ into incubator	8	12.9	7	11.6
O ₂ into hood	5	8.0	3	5.0
CPAP	38	61.3	40	66.7
SIMV	11	17.8	10	16.7
Total	62	100	60	100

hiPDA: Hemodynamically insignificant patent ductus arteriosus, hsPDA: Hemodynamically significant patent ductus arteriosus, CPAP: Continuous positive airway pressure, SIMV: Synchronized intermittent mandatory ventilation

Table 2. Difference in O₂ need of patients with hemodynamically significant patent ductus arteriosus before and after pharmacologic patent ductus arteriosus closure

	Before PDA closed		After PDA closed		p
	n	(%)	n	(%)	
O ₂ into incubator	7	11.7	9	15.5	0.033
O ₂ into hood	3	5	8	13.8	
CPAP	40	66.6	33	56.9	
SIMV	10	16.7	8	13.8	
Total	60	100	58 ^s	100	

PDA: Patent ductus arteriosus, CPAP: Continuous positive airway pressure, SIMV: Synchronized intermittent mandatory ventilation, Two patients were not included because of surgical closure

Table 3. Ratio of left atrium to aortic root and ductal diameters of patients

	hiPDA	hsPDA	p
LA:Ao	1.11±0.48	1.36±0.27	<0.0001
Ductal diameter (mm)	1.65±0.32	2.25±0.44	<0.0001

hiPDA: Hemodynamically insignificant patent ductus arteriosus, hsPDA: Hemodynamically significant patent ductus arteriosus, LA:Ao: Ratio of left atrium to aortic root

Table 4. Relationship between O₂ requirement, ratio of left atrium to aortic root, ductal diameter and required course number of ibuprofen to close patent ductus arteriosus in patients

	1 course		2 courses		3 courses		p
	n	%	n	%	n	%	
O ₂ into incubator	7	11.5	3	5.0	-	-	0.508 (χ ² =2.321)
O ₂ into hood	3	5.0	1	1.7	-	-	
CPAP	32	53.3	2	3.5	1	1.7	
SIMV	7	11.5	3	5.0	1	1.7	
	1 course		2 courses		3 courses		p
	1.35±0.28		1.43±0.21		1.46±0.19		
Ductal diameter (mm)	2.18±0.36		2.62±0.65		2.76±0.55		0.381

CPAP: Continuous positive airway pressure, SIMV: Synchronized intermittent mandatory ventilation, LA:Ao: Ratio of left atrium to aortic root

reported no difference in respiratory parameters (16,17) after pharmacologic closure of PDA. It is hard to show the isolated effect of PDA closure on respiratory system due to co-affecting factors especially like worsening or ameliorating respiratory distress syndrome, but our study supports that a significant difference in O₂ requirement of premature infants could be provided with pharmacological PDA closure (Table 2).

Echocardiographic criteria, such as left ventricular outflow/superior vena cava flow ratio, diastolic and mean flow velocities of the left pulmonary artery, but especially DD and LA:Ao, were found to be adequate and reliable markers of hsPDA (18,19). In our study, DD and LA:Ao were found to be significantly higher in premature infants who needed treatment than in those PDA closed spontaneously (Table 3). This suggests that DD and LA:Ao reflect hemodynamic significance of PDA and could be used in estimating the necessity of pharmacologic treatment of PDA.

Response to pharmacologic agents that were administered to close PDA is related with GA and/or birth weight but do not depend only on those. Despite spontaneous ductus closure in some extremely immature premature infants, some premature large-for-gestational-age infants do not respond to one course of ibuprofen and require additional courses or surgical intervention (20,21). There are multiple factors affecting ductus closure. In our study, the number of ibuprofen courses required to close PDA was not found to be associated with O₂ requirement but with DD (Table 4). This suggests that anatomic size of PDA is the most reliable criterion in defining hsPDA and could be used to estimate the duration of treatment to close PDA.

Although high rates of pharmacologic closure are achieved with ibuprofen, it is not completely safe. Paracetamol may be a medical alternative in the management of PDA (22). Paracetamol was used successfully for PDA closure in our two patients who had contraindications for ibuprofen.

Conclusion

In conclusion, there is a need for an international consensus on criteria for defining hsPDA. Oxygen requirement of premature infants is not different between patients with hsPDA and hiPDA but decreases by PDA closure. Echocardiographic criteria seem more reliable than respiratory criteria in predicting hsPDA and, ductus diameter should also be used to estimate the duration of treatment. Further studies are needed to evaluate the value of each criterion in defining hsPDA.

Ethics

Ethics Committee Approval: Atatürk University, Ethics Committee of Medicine Faculty, 18.08.2011, meeting number 7, Decision number 19.

Peer-review: Internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: İrfan Oğuz Şahin, Canan Yolcu. Concept: İrfan Oğuz Şahin, Haşim Olgun, Naci Ceviz. Design: İrfan Oğuz Şahin, Canan Yolcu. Data Collection or Processing: İrfan Oğuz Şahin, Mustafa Kara, Yaşar Demirelli. Analysis or Interpretation: İrfan Oğuz Şahin, Ayşegül Elbir Şahin. Literature Search: İrfan Oğuz Şahin, Ayşegül Elbir Şahin. Writing: İrfan Oğuz Şahin, Haşim Olgun, Naci Ceviz.

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