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Short-term Course of PDA in Preterm Infants with RDS and Factors Associated with its Persistence

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Abstract

Background: Patent ductus arteriosus (PDA) refers to the continued existence postnatally of the fetal link (ductus arteriosus) connecting the aorta and the pulmonary artery. ***Objective***: determine whether the surfactant replacement therapy used for the treatment of respiratory distress syndrome (RDS) is affecting the incidence and the closure of PDA. Also to study the different treatment strategies for RDS and PDA and its effects on the PDA closure in preterm infants. ***Methods***: A prospective observational study done in the neonatal intensive care unit in a tertiary center in Baghdad, Iraq. The study was conducted from July 2024 to February 2025. The patients included in the study are all preterm infants less than 37 weeks' gestational age who were diagnosed with RDS and treated for that by either nasal continuous positive airway pressure (CPAP), mechanical ventilation (MV), or both. ***Results***: 43 preterm infants were included with a median gestational age at labor of 30 (IQR=8-33) weeks; birth weight ranged between 750 and 2250 grams with a median of 1400 grams (IQR=1100-1900). Males were the dominant contributor, accounting for 60.5%. Only 20.9% of infants were breastfed, 46.5% were on formula, and 32.6% received mixed feeding. The closure of PDA occurred in 15 (34.9%) infants, while closure failed (persistent PDA) in 10 (23.3%) and 18 (41.9%) remained with no PDA. ***Conclusions***: There was no difference in the treatment of PDA between infants who received surfactant and those who received respiratory support with NCPAP or MV, despite the increased number of closed PDAs in treated infants; however, there was a significant difference in PDA closure based on whether the infants received treatment.

Keywords: Mechanical ventilation; NCPAP; Patent ductus arteriosus; Respiratory support; Surfactant.

المسار قصير الأمد للقناة الشريانية السالكة لدى الأطفال الخدج المصابين ب RDS والعوامل المرتبطة باستمراره

الخلاصة

الخلفية: يشير القناة الشريانية السالكة (PDA) إلى استمرار وجود الرابط الجنيني (القناة الشريانية) الذي يربط الشريان الأورطي بالشريان الرئوي بعد الولادة. **الهدف**: تحديد ما إذا كان العلاج البديل للمواد السطحية المستخدم لعلاج متلازمة الضائقة التنفسية (RDS) يؤثر على حدوث و/أو إغلاق القناة الشريانية السالكة ودراسة استراتيجيات العلاج المختلفة ل RDS وPDA وتأثيره على إغلاق PDA لدى الأطفال الخدج. **الطرائق**: دراسة رصدية مستقبلية أجريت في وحدة العناية المركزة لحديثي الولادة في مركز ثالثي في بغداد، العراق خلال الفترة من يوليو 2024 إلى فبراير 2025. جميع المرضى المشمولين في الدراسة هم من الرضع الخدج الذين تقل أعمارهم عن 37 أسبوعا من الحمل، وتم تشخيصهم بمرض RDS وعولجوا إما بضغط الهواء الإيجابي المستمر للأنف (CPAP)، أو التهوية الميكانيكية (MV)، أو كليهما. **النتائج**: تم تضمين 43 رضيعا خدجا بمتوسط عمر حمل عند الولادة 30 (IQR=8-33) أسبوعا؛ تراوح وزن الولادة بين 750 و2250 جراما مع متوسط 1400 جرام (IQR=1100-1900). كان الذكور المساهم الرئيسي، حيث ساهموا بنسبة 60.5٪. فقط 20.9٪ من الأطفال رضعوا رضاعة طبيعية، و46.5٪ كانوا على حليب صناعي، و32.6٪ تلقوا تغذية مختلطة. حدث إغلاق اضطراب الPDA لدى 15 رضيعا (34.9٪)، بينما فشل الإغلاق (PDA المستمر) في 10 (23.3٪) و18 (41.9٪) بقوا بدون PDA. **الاستنتاجات**: لم يكن هناك فرق في علاج PDA بين الرضع الذين تلقوا مواد فعالة للتوتر السطحي وأولئك الذين تلقوا دعم تنفسي باستخدام NCPAP أو MV، على الرغم من زيادة عدد الPDA المغلقة لدى الرضع المعالجين؛ ومع ذلك، كان هناك فرق كبير في إغلاق PDA بناء على ما إذا كان الرضع قد تلقوا العلاج.

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INTRODUCTION

Patent ductus arteriosus (PDA) refers to the continued existence postnatally of the fetal link (ductus arteriosus) connecting the aorta and the pulmonary artery [1]. In the absence of further anatomical heart anomalies or increased pulmonary vascular resistance, the shunt in PDA will be oriented from left to right (from the aorta to the pulmonary artery) [2]. Manifestations may encompass inadequate growth, suboptimal nutrition, rapid heart rate, and accelerated breathing. A persistent murmur at the left upper sternal border and pronounced pulses are frequently observed [3]. The management of RDS relies on administration of exogenous surfactants and postnatal respiratory support modalities such as nasal continuous positive airway pressure (NCPAP) and mechanical ventilation, which significantly influences cardiac hemodynamics [4]. While surfactant therapy improves alveolar recruitment and pulmonary compliance, the rapid decline in pulmonary vascular resistance immediately post-administration can unmask or exacerbate ductal shunting [5]. Diagnostic accuracy is therefore of paramount importance; serial bedside echocardiography has emerged as the gold standard method for dynamic assessment, allowing clinicians to classify ductal magnitude and identify hemodynamically significant PDAs requiring targeted intervention [6,7]. Despite established global guidelines utilizing nonsteroidal anti-inflammatory drugs (NSAIDs) like ibuprofen or acetaminophen, therapeutic strategies remain highly heterogenous[8,9] . In resource-limited environments and tertiary care settings across the Middle East,

including Iraq, localized prospective data tracking the longitudinal evolution of PDA from the hyperacute post-surfactant phase (24 hours) through early hospitalization (one week) to ultimate discharge are strikingly sparse [10]. Therefore, this prospective observational study was designed to characterize the dynamic clinical course and progression of PDA in a cohort of preterm infants admitted with RDS to a tertiary neonatal intensive care unit in Baghdad, Iraq. Specifically, we aimed to map serial echocardiographic changes across three distinct clinical timeframes and determine the impact of various therapeutic interventions—including respiratory support modalities, conservative management, ibuprofen, and acetaminophen—on rates of ductal closure.

METHODS

Study design and setting

This is a prospective observational study done in the Neonatal Intensive Care Unit (NICU) in a tertiary center in Baghdad, Iraq. Through the period from July 2024 to February 2025.

Inclusion criteria

The patients included in the study are all preterm infants less than 37 weeks' gestational age who were diagnosed with RDS and treated for that by either nasal CPAP, MV, or both.

Intervention and outcome measurements

The questionnaire form, which included maternal and neonatal characteristics, was taken from the patient's files and by directly questioning the parents or caregivers. Some may need exogenous surfactant administration according to their clinical conditions, chest X-ray findings, and respiratory support. Echocardiograms were done at the age of 24 hours after starting treatment for RDS, one week for those who had PDA, and on discharge. Echocardiograms were done by a portable echo device by pediatric cardiologists, and the PDA is categorized as small (less than 1.5 mm in diameter), moderate (1.5-3 mm in diameter), or large (more than 3 mm in diameter). A hemodynamically significant PDA is usually a moderate- to large-sized PDA with echocardiographic findings (left atrium to aortic ratio of more than 1.4-1.5, predominant left-to-right shunt, unrestrictive ductal flow, left ventricular volume overload, diastolic flow reversal, and clinical signs of pulmonary overcirculation or systemic hypoperfusion). Treatment for PDA: either received no treatment, was managed conservatively by just fluid restriction and monitoring the clinical condition, or may receive medical treatment with oral ibuprofen (10 mg/kg initially, then 5 mg/kg at 24 and 48 hours) or oral or IV (15 mg/kg every 6 hours for 3-7 days). The treatment selection varies depending on the treatment physician.

Ethical considerations

The study protocol was approved by the local Research Ethics Committee of the College of Medicine, University of Baghdad (IRB 25 on 10 September 2025). A signed consent was obtained from the parents before their enrollment in the study.

Statistical analysis

Data were entered, managed, and analyzed using the statistical package for social sciences (SPSS) version 28. Variables were presented as frequencies, percentages, and median and interquartile range according to the type of variable. The overall significance of changes in the frequency of PDA across the time points (24 hours after surfactant, one week and on discharge) was assessed with Cochran's Q test. Furthermore, we performed pairwise comparisons using McNemar's test to evaluate the difference between each pair of time points (twenty-four hours vs. one week, twenty-four hours vs. discharge, and one week vs. discharge). The association between the dependent variable (PDA status) and independent variables (treatment and therapeutic strategies) was tested through cross-tabulation using Fisher's exact test and chi-square test when they were applicable. All statistical tests and procedures were initiated at a level of significance of < 0.05.

RESULTS

In this study, 43 preterm infants were included with a median gestational age at labor of 30 (IQR: 28-33) weeks; birth weight ranged between 750 and 2250 grams with a median of 1400 (IQR: 1100-1900) grams. Males constituted most of the studied population (60.5%). Regarding feeding practices, 20.9% of infants received exclusive breast milk, 46.5% were exclusively formula-fed, and 32.6% received mixed feeding. Dysmorphic/congenital abnormalities (1 spina bifida, 2 hydrocephalus, and 1 cystic hygroma) were found in 4 infants (9.3%); additionally, maternal characteristics are shown in the same table (Table 1).

Table 1: Maternal and infant baseline characteristics in the sample studied (n=43)

Characteristics	Variables	values
Gestational age (week) median		30(28-33)
Birth weight (gram) median		1400(1100-1900)
Sex of neonate	Male	26(60.5)
	Female	17(39.5)
	Ratio	1.5:1.0
Type of feeding	Breast feeding	9(20.9)
	Formula	20(46.5)
	Mixed	14(32.6)
Dysmorphic/congenital abnormalities		4(9.3)
Obstetric history, median (IQR)	Gravidity	4(2-5)
	Parity	3(2-4)
	Abortion	1(0-2)
Maternal comorbidity	Diabetes mellitus	8(18.6)
	Hypertension	12(27.9)
	Thyroid disease	3(7.0)

Values are presented as IQR and n(%). IQR: Interquartile range; *Spina bifida 1; Hydrocephalus 2; Cystic hygroma 1.

Table 2 summarizes the frequency distribution and duration of respiratory support and therapeutic strategies; infants who received surfactant were 36 (83.7%) at a median age of 4 hours; however, none of the infants had repeated surfactant. The NCPAP was used in 39 infants for a median duration of 3 days, and MV in 31 (72.1%) for a median duration of 2.5 days.

Table 2: Frequency distribution and duration of respiratory support and therapeutic strategies

Variables	Value
Infant Received surfactant n(%)	36(83.7)
Age of giving surfactant (hours), median (IQR)	4(2-5)
NCPAP n(%)	39(90.7)
Duration of NCPAP, median (IQR) (day)	3(3 - 5)
Mechanical ventilation (MV), n (%)	31(72.1)
Duration of MV, median (IQR) (day)	2.5(2 - 4)

IQR: Interquartile range; NCPAP: nasal continuous positive airway pressure.

Echocardiography examinations at different time points revealed that at 24 hours after surfactant, a small PDA was reported in 21 (48.8%) infants, and a moderate PDA in 3 (7.0%), giving a total PDA of 24 (55.8%). After one week of surfactant, PDA was reported in a total of 22 (51.2%), ASD II in 41.9%, PFO in 4.7%, and mild PH in only one infant, while 10 infants had normal echography; however, 10 infants had combined PDA and ASD II. On discharge, 10 infants remained with PDA; 9 of them were combined with ASD II (Table 3).

Table 3: Frequency distribution of echocardiography findings at different time points

Time point	Echocardiographic findings	n(%)
Twenty-four hours after surfactant use	Small PDA	21(48.8)
	Moderate PDA	3(7)
	Normal	19(44.2)
One week after surfactant use	PDA	12(27.9)
	PDA + ASD II	10(23.3)
	ASD II	8(18.6)
	PFO	2(4.7)
	Mild PH	1(2.3)
	Normal	10(23.3)
On Discharge	PDA	1(2.3)
	PDA + ASDII	9(20.9)
	ASD II	7(16.3)
	PFO	2(4.7)
	Normal	24(55.8)

ASD: atrial septal defect; ASD II: ASD secundum; PFO: Patent foreman ovale; PDA: patent ductus arteriorous; PH: pulmonary hypertension.

Furthermore, in general, the frequency of PDA at different time points was compared; it had been significantly found that the number of infants with PDA reduced from 24 at 24 hours after surfactant to 22 at one week and only 10 on discharge ($p<0.001$). On the other hand, the change in the number of PDAs at one week was not significantly different than that at 24 hours after surfactant, but on discharge, the number of PDAs was significantly lower than that at one week and at 24 hours after surfactant ($p<0.001$) on pairwise comparisons (Table 4). The PDA status as an outcome showed that closure of PDA occurred in 15 (34.9%) infants, while closure failed (persistent PDA) in 10 (23.3%) and 18 (41.9%) remained with no PDA, as shown in Figure 1. Cross-tabulation to assess the correlation between PDA status from one side as a dependent variable against treatment and therapeutic strategies on the other side as predictor (independent) variables of closure.

Table 4: Changes in patent ductus arteriosus frequency following surfactant administration

PDA status	24 hours	1 week	At discharge
PDA n(%)	24(55.8)	22(51.2)	10(23.3)
NO PDA n(%)	19(44.2)	21(48.8)	33(76.7)
Cochran's comparison Q=22.933, df=2, $p<0.001$			
Pair wise comparisons (McNemar test)			
Comparison	***p-value***		
24 hours *vs*. 1 week	0.62		
24 hours *vs*. discharge	<0.001		
1 week *vs*. discharge	<0.001		

PDA: Patent ductus arteriosus.

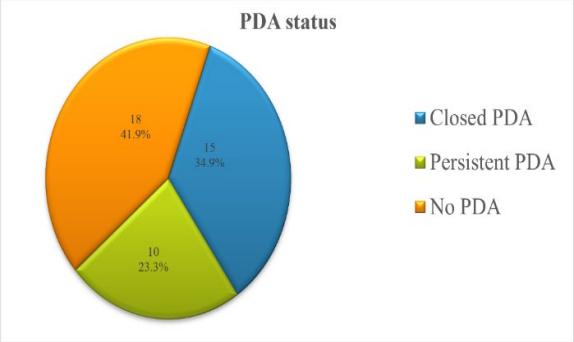


Figure 1: Distribution of PDA closure, persistent PDA, and absence of PDA throughout follow-up.

This analysis showed that surfactant given and respiratory support with NCPAP or MV were not significantly affecting the closure of PDA ($p> 0.05$). Conversely, closure of PDA was significantly affected by receiving treatment for PDA ($p< 0.001$), where among the 24 infants who received treatment for PDA, 14 (58.3%) had closed PDA on discharge compared to only 1 (5.3%) among those who did not receive treatment for PDA. From another point of view, the higher rate of closure of PDA was reported among infants who received ibuprofen (75%) compared to 66.7% among those on conservative treatment, 50 among those who received paracetamol, and only 5.3% among those who did not receive treatment for PDA ($p< 0.001$) (Table 5).

DISCUSSION

In this prospective observational study of preterm infants with RDS, serial echocardiographic evaluation demonstrated a significant longitudinal reduction in PDA prevalence from the hyperacute post-surfactant phase to hospital discharge ($p< 0.001$). Crucially, active pharmacological intervention was the principal determinant of ductal closure ($p< 0.001$), with treated infants achieving a 58.3% closure rate at discharge compared to only 5.3% among untreated infants. Furthermore, oral ibuprofen demonstrated the highest closure rate (75.0%), outperforming conservative management (66.7%) and paracetamol/acetaminophen (50.0%).

Table 5: Cross-tabulation for the correlation between treatment strategies for RDS and PDA with the PDA closure in preterm infants (n=43)

Variables	Category	Closed PDA	Persistent PDA	No PDA	*p*-value
Surfactant given	Yes	13(36.1)	8(22.2)	15(41.7)	1.0[f]
	No	2(28.6)	2(28.6)	3(42.9)	
Respiratory support-NCPAP	Yes	15(38.5)	9(23.1)	15(38.5)	0.267[f]
	No	0(0.0)	1(25)	3(75)	
Respiratory support-MV	Yes	10(32.3)	7(22.6)	14(45.2)	0.759[f]
	No	5(41.7)	3(25)	4(33.3)	
Received treatment for PDA	Yes	14(58.3)	10(41.7)	0(0.0)	<0.001[c]
	No	1(5.3)	0(0.0)	18(94.7)	
Medication Received	Conservative	4(66.7)	2(33.3)	0(0.0)	<0.001[f]
	Paracetamol	7(50)	7(50)	0(0.0)	
	Ibuprofen	3(75)	1(25)	0(0.0)	
	None	1(5.3)	0(0.0)	18(94.7)	

Values are presented as frequency and percentage. [c] Chi-square test; [f] Fisher's exact test. MV: Mechanical ventilation; NCPAP: nasal continuous positive airway pressure.

These findings highlight both the natural dynamic evolution of ductus architecture in premature neonates and the vital necessity of timely, targeted pharmacological management in tertiary neonatal intensive care settings. In the current study, the frequency of PDA had significantly reduced after surfactant administration. This aligns with results from a recent meta-analysis: preterm infants who got Poractant-alfa had a significantly lower incidence of PDA requiring hemodynamic therapy. This conclusion was drawn from 12 studies, including 1472 participants. The meta-analysis demonstrated a physio-pathological connection between surfactant use and PDA. But whether this surfactant effect on PDA incidence could result in a clinically significant benefit is still unknown [11]. In this study, respiratory support with NCPAP or MV did not significantly affect the closure of PDA; despite the increased number of closed PDAs in treated infants, the finding may be due to the small sample size of the current study. This match finding was demonstrated by Cucerea *et al*., who concluded that there is no significant difference in PDA treated with surfactants in infants with a gestational age of <32 weeks assessed in the first 24 hours of life [12]. At hospital discharge, the closure of PDA in the current study was significantly associated with receipt of PDA-directed treatment. When analyzed according to the type of treatment, PDA closure was observed in 75% of infants who received ibuprofen. This closure rate was higher than that reported by Gupta et al., who found that a single early course of ibuprofen resulted in a closed or small PDA in 55% of infants who received ibuprofen in a double-blind, randomized, placebo-controlled trial as assessed by echocardiography at 3 weeks of age [13]. The difference in closure rate could be attributed to differences in study population and clinical characteristics. In particular, the study by Gupta *et al*. included extremely preterm infants with large-size PDA, a population at higher risk of persistent ductal patency and potentially less responsive to pharmacological closure [14,15]. Paracetamol has emerged as a potential alternative to conventional pharmacological agents, such as ibuprofen and indomethacin, for treatment of PDA in preterm infants. Santos et al. reported successful treatment of PDA with paracetamol in preterm infants and suggested its potential use as an alternative to ibuprofen or indomethacin [16]. In addition, Ohlsson *et al*. demonstrated the similar efficacy and safety profile of paracetamol to ibuprofen and indomethacin, with relatively few reported adverse effects [17]. Therefore, paracetamol may represent a therapeutic option, particularly in infants in whom ibuprofen or indomethacin is contraindicated or poorly tolerated [18]. Comparative evidence has also demonstrated broadly similar efficacy among the available pharmacological agents. Two meta-analyses found no statistically significant difference in PDA closure rates between oral ibuprofen and intravenous indomethacin, while another meta-analysis similarly reported no significant difference between oral ibuprofen and either oral or intravenous indomethacin [19–21]. Regarding the need for surgical ligation, three pooled analyses found no significant differences between either of the medical options [22]. Collectively, these findings suggest that ibuprofen, indomethacin, and paracetamol may have comparable efficacy for PDA closure in selected preterm infants. The choice of agent may reasonably depend on gestational age, clinical status, contraindications adverse-effect profiles, route of administration, and local treatment protocols.

Study Limitations

Several limitations must be acknowledged when interpreting the results of this study. First, the small sample size (n=43) from a single tertiary care center limits statistical power for subgroup interactions and restricts the generalizability of the results. Second, since the treatment allocation (ibuprofen vs. acetaminophen vs. conservative management) was non-randomized and based on individual treating physician discretion, selection bias cannot be ruled out. Future prospective multicenter randomized controlled trials within regional NICUs are warranted to validate these comparative drug efficacies and establish standardized local treatment algorithms for PDA management in Iraq.

Conclusion

PDA-directed pharmacological treatment was significantly associated with PDA closure at discharge. Neither surfactant administration nor respiratory support was significantly associated with PDA closure.

Conflict of interests

The authors declared no conflict of interest.

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The authors did not receive any source of funds.

Data sharing statement

The data that supports the findings of this study are available from the corresponding author upon a reasonable request.

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