Use of Intravenous Acetaminophen as a Medical Treatment for Closure of Patent Ductus Arteriosus in Preterm Neonates

A Single-Center Clinical Observational Study

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ABSTRACT

Background: The common cardiovascular disorder in premature neonates is patent ductus arteriosus (PDA). The spontaneous closure of patent ductus arteriosus is common. Intravenous paracetamol has shown efficacy in the closure of patent ductus arteriosus under different situations.

Objectives: To evaluate the efficacy of intravenous paracetamol in closure of patent ductus arteriosus in preterm neonates.

Methods: A prospective study conducted at Baghdad Teaching Hospital, Children Welfare Teaching Hospital, and Nursing Hospital during a period of six months from 1st of February to 1st of August 2024. It included 45 preterm neonates (gestational age < 37 weeks) with patent ductus arteriosus admitted for respiratory symptoms. Patent ductus arteriosus was diagnosed by echocardiography. All neonates received paracetamol at a dose of 15 mg/kg/dose intravenously, every six hours for five days. All neonates underwent echocardiography with all views before management and one day after the last dose of paracetamol.

Results: In this study, closure of patent ductus arteriosus occurred in 28 neonates, giving a rate of 62.2%. The rate of non-closure was significantly higher in neonates delivered with a gestational age of < 30 weeks, birth weight of < 1500 g, whose mothers did not receive antenatal steroids or had hypertension, neonates with moderate patent ductus arteriosus size, and those who received two sessions of paracetamol therapy.

Conclusion: Paracetamol is effective in closure of PDA in preterm neonates of < 34 weeks. Some neonates with PDA required two courses of the trial drug for closure.

Keywords: Paracetamol; Patent ductus arteriosus; Preterm, Iraq.

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The ductus arteriosus is a fetal vessel that allows the oxygenated blood from the placenta to bypass the lungs in utero[(1)]. The ductus constricts because of elevated arterial oxygen tension and reduced flow via the ductus arteriosus. In the premature infant, the ductus arteriosus does not close rapidly and may require pharmacologic or surgical closure to treat side effects[(2)].

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The most prevalent cardiovascular condition among preterm newborns is patent ductus arteriosus (PDA), which has an inverse relationship with gestational age at birth. Based on data from term newborns, PDAs are estimated to occur in approximately 1 in 2000 births, which makes up 5% to 10% of all congenital heart disease[(3)].

According to recent research, more than 50% of neonates born at less than 26 weeks of gestation had PDA after two months of life. Moreover, Infants born weighing less than 1000 grams are at the highest risk for PDA. In this population, 70% will have a PDA on day 7[(4)]. Some genetic

conditions are associated with PDA: Trisomy 13, 18, 21; Holt-Oram, DiGeorge, and familial PDA[5]. Maternal conditions associated with PDA include maternal diabetes and calcium channel blockers. Neonatal conditions include extreme prematurity, respiratory distress syndrome, sepsis, loop diuretics, aminoglycosides, cimetidine, and heparin[6]. The PDA is asymptomatic. At times, the patient may report decreased exercise tolerance or pulmonary congestion in conjunction with a murmur[7]. The classic PDA murmur is a continuous, “machinery” murmur with wide pulse pressure, hypotension, hepatomegaly and signs of pulmonary edema [8]. The diagnosis of PDA is almost always based on clinical evaluation, pulse oximetry/arterial blood gas (ABG) analysis, chest radiographs, electrocardiography and echocardiographic assessment, in which ductus size alone is inadequate to attribute hemodynamic significance. The exact diameter at which hemodynamic significance will occur varies by patient and postnatal age, depending on body size and many other factors, as oxygen saturation, surfactant administration, and furosemide[9]. With a large left-to-right shunt, indirect signs of obligate pulmonary hypertension may often be seen[10].

There is an increasing interest in the use of paracetamol for PDA closure in preterm infants. Inhibiting the peroxidase moiety of paracetamol results in the vasoconstrictive impact on ductal tissue, which prevents prostaglandin synthesis[11]. Paracetamol has demonstrated efficacy in PDA closure in different situations, particularly when NSAIDS either are contraindicated or have failed to achieve PDA closure. Paracetamol is an effective and well-tolerated first-line drug treatment for PDA in premature infants[12].

Methods

A clinical observational study conducted at Baghdad Teaching Hospital (Department of Obstetrics and Gynecology and Neonatal Nursery Unit), Children Welfare Teaching Hospital, and Nursing Home Hospital for six months from 1st of February to 1st of August 2024.

The study included 45 preterm neonates (gestational age < 37 weeks) admitted for respiratory signs and had hemodynamically significant PDA or patients who had isolated PDA. The sample size was determined to accurately estimate the patent ductus arteriosus closure rate, ensuring reliable statistical power. Nevertheless, the small sample size may induce bias and reduce accuracy, resulting in wider confidence ranges and a higher probability of random error.

Exclusion criteria

- Patients with thrombocytopenia (< 50,000 / mm^3).
- Patients with intracranial hemorrhage (ICH) or sepsis.
- Patients with blood urea nitrogen > 14 mmol/L.
- Ductal-dependent congenital heart diseases.

A structured questionnaire was utilised to collect data on the participants' age, gender, gestational age (in weeks), birth weight, maternal parity, obstetric history (including gestational diabetes mellitus, mothers receive antenatal steroids, and hypertension), the presence of other congenital heart defects, the size of the PDA, and the number of paracetamol treatment sessions. All neonates received paracetamol dose at 15 mg/kg/dose intravenously every six hours for five days[13].

In this study, all neonates underwent echocardiography examination with all views before management and one day after the last dose of paracetamol. These examinations were done by different devices (Vino G50, GE LOGIQe and Phillips Cx50 machines), the following parameters were examined:

- Ductus arteriosus characteristics, such as ductus arteriosus size (Small < 1.5

mm, moderate 1.5 – 2 mm and large > 2 mm) [14].

- Flow direction (Left to right, right to left, or bidirectional).
- Assessment of pulmonary circulation:
- Dilated left side of the heart on visual inspection (eyeballing) and LA/Ao ratio: Mild < 1.4, moderate 1.41 – 1.6 and severe > 1.6).
- Assessment of systemic hypoperfusion.
- left ventricular end diastolic diameter (LVEDD) correlate with Z scores, as shown below;

$$Z = \frac{\text{measured LVEDD} - \text{mean LVEDD reference}}{\text{SD reference}}$$

Z-score of 0 means the measurement is exactly average.

Positive Z-scores indicate a larger LVEDD than expected.

Negative Z-scores indicate a smaller LVEDD.

Normal ranges

Z-score	Interpretation
−2 to +2	Normal range
< −2	Below normal (possibly hypoplastic or underfilled LV)
> +2	Above normal (dilated LV)

Verbal permission was obtained from each parent prior to collecting data, and information were anonymous. Names were removed and replaced by identification codes. All information kept confidential in a password secured laptop and data used exclusively for the research purposes. Administrative approvals were granted from Baghdad Teaching Hospital (Department of Obstetrics and Gynecology and Neonatal Nursery Unit), Children Welfare Teaching Hospital, and Nursing Home Hospital.

The data was analyzed using Statistical Package for Social Sciences (SPSS) version 25. The data were presented as mean, standard deviation, and ranges. Frequency and percentages presented the categorical data. The significance of the difference in different percentages (qualitative data) was tested using the Pearson Chi-square test (χ^2-test) with the application of Yates' correction or Fisher's Exact test whenever applicable. A level of P-value less than 0.05 was considered significant[15].

Results

Forty-five pre-term infants with PDA suspected clinically and confirmed by echocardiography were recruited in this study. All of them received intravenous paracetamol, then they were assessed clinically and by echocardiography to confirm PDA closure. The age range of neonates was 2 to 18 days (only three cases were more than 10 days) with a mean of 4.27 ± 1.29 days; of them, 62.2% of neonates were ≤ 3 days. Regarding gender, 46.7% of them were males, with a ratio of 1:114. The mean gestational age was 31.2 ± 2.70 weeks, and 33.3% were delivered with a gestational age of < 30 weeks. The mean birth weight was 1601 ± 473 g, and 44.4% had a birth weight of < 1500 g. Concerning parity, 48.8% of women had a parity history of 1-3 children, while the other 51.2% had a history of ≥ 4. Also, 75.6% of neonates were delivered through cesarean sections. During the last pregnancy, 60% of mothers received antenatal steroids. A history of maternal hypertension and diabetes was reported by 20% and 22.2%, respectively. Other types of congenital heart defects, such as atrial septal defect, ventricular septal defect, and patent foramen ovale, were detected in 84.4% of neonates. Small PDA size was detected in 77.8% of neonates, while the remaining 22.2% had moderate PDA. About 55.6% of neonates needed one session of paracetamol treatment, while the other 44.4% needed two sessions, (Table 1).

Table 1: Distribution of the study group according to baseline and related characteristics.

Neonates' characteristics	No. (n= 45)	Percentage
Age (days)		
≤ 3	28	62.2
> 3	17	37.8
Gender		
Male	21	46.7
Female	24	53.3
Gestational Age (Weeks)		
< 30	15	33.3
≥ 30	30	66.7
Birth weight (g)		
< 1500	20	44.4
≥ 1500	25	55.6
Parity		
1 – 3	22	48.8
≥ 4	23	51.2
Mode of Delivery		
Normal Vaginal Delivery	11	24.4
Cesarean Section	34	75.6
Antenatal Steroids		
Yes	27	60.0
No	18	40.0
Gestational Diabetes		
Yes	9	20.0
No	36	80.0
Hypertension		
Yes	10	22.2
No	35	77.8
Accompanied with other congenital heart defects (ASDII, PFO, VSD)		
Yes	38	84.4
No	7	15.6
PDA Size		
Small	35	77.8
Moderate	10	22.2
Number of Sessions		
One	25	55.6
Two	20	44.4

Table 2: Distribution of the study group according to baseline characteristics and PDA closure.

Neonates' characteristics		PDA Closure		Total (n= 45) No. (%)	P- Value*
		Closed (n= 28) No. (%)	Not closed (n= 17) No. (%)		
Age (days)	≤ 3	18 (64.3)	10 (35.7)	28 (62.2)	**0.741**
	> 3	10 (58.8)	7 (41.2)	17 (37.8)	
Gender	Female	14 (58.3)	10 (41.7)	24 (53.3)	**0.565**
	Male	14 (66.7)	7 (33.3)	21 (46.7)	
Gestational age (weeks)	< 30	6 (40.0)	9 (60.0)	15 (33.3)	**0.029**
	≥ 30	22 (73.3)	8 (26.7)	30 (66.7)	
Birth weight (g)	< 1500	9 (45.0)	11 (55.0)	20 (44.4)	**0.033**
	≥ 1500	19 (76.0)	6 (24.0)	25 (55.6)	
Parity	1 – 3	12 (54.5)	10 (45.5)	22 (48.9)	**0.298**
	≥ 4	16 (69.6)	7 (30.4)	23 (51.1)	
Mode of delivery	Vaginal	9 (81.8)	2 (18.2)	11 (24.4)	**0.123**
	Cesarean section	19 (55.9)	15 (44.1)	34 (75.6)	
Antenatal steroids	Yes	21 (77.8)	6 (22.2)	27 (60)	**0.008**
	No	7 (38.9)	11 (61.1)	18 (40)	
Gestational diabetes	Yes	4 (44.4)	5 (55.6)	9 (20.0)	**0.218**
	No	24 (66.7)	12 (33.3)	36 (80.0)	
Hypertension	Yes	3 (30.0)	7 (70.0)	10 (22.2)	**0.017**
	No	25 (71.4)	10 (28.6)	35 (77.8)	
Other congenital heart defects	Yes	24 (63.2)	14 (36.8)	38 (84.4)	**0.763**
	No	4 (57.1)	3 (42.9)	7 (15.6)	
PDA size	Small	26 (74.3)	9 (25.7)	35 (77.8)	**0.001**
	Moderate	2 (20.0)	8 (80.0)	10 (22.2)	
Number of sessions	One	22 (88.0)	3 (12.0)	25 (55.6)	**0.001**
	Two	6 (30.0)	14 (70.0)	20 (44.4)	

* The p-value difference between numbers was calculated using Pearson Chi-square test.

All 45 neonates were assessed for the closure of PDA, and we found that closure of PDA occurred in 28 neonates, giving a rate of 62.2%.

This study found that the rate of PDA non-closure was significantly higher in neonates with a gestational age of < 30 weeks (60%, P= 0.029), birth weight of < 1500 g (55%, P= 0.033), whose mothers didn't receive antenatal steroids (61.1%, P= 0.008), or had hypertension (70%, P= 0.017), moderate PDA size (80%, P = 0.001), and those who received two sessions of paracetamol therapy (70%, P = 0.001). Other characteristics revealed no significant difference according to the status of PDA closure (P ≥ 0.05), (Table 2).

There was no significant association between the PDA size and the number of paracetamol sessions (P= 0.262), (Table 3).

Table 3: Distribution of the study group according to PDA size and number of sessions.

Number of Sessions	PDA Size		Total (n= 45) No. (%)	P- Value*
	Small (n= 35) No. (%)	Moderate (n= 10) No. (%)		
One	4 (16.0)	21 (84.0)	25 (55.6)	**0.262**
Two	6 (30.0)	14 (70.0)	20 (44.4)	

* The p-value between numbers was calculated by using a chi-square test with Yate's correction.

Discussion

All 45 neonates enrolled in this study were assessed for the closure of PDA, and results revealed that closure of PDA occurred in 62.2% of neonates. As compared to other studies, a better closure rate for infants with PDA was found in Stremming et al.'s study, as they found that 80% of patients treated with paracetamol had their ductus closed[16]. In the same concern, ALSuwayfee et al study reported that the success rate of PDA closure ranged between 70-100% using oral or intravenous paracetamol after 48 h of postnatal age[17]. Afif et al.'s study concludes that there may be a role for intravenous paracetamol in late closure of infants with a significant PDA to avoid ligation, in which paracetamol was associated with immediate closure in 25% of infants, while no response in 11%. In 64% of them, the PDA constricted[18]. The different rates are multifactorial; it may relate to the different sample size or study design or might be related to the difference in the gestational age at the time of drug use, size of duct (larger ductus is harder to close with pharmacologic treatment, the timing of paracetamol administration and the presence of other concomitant diseases. There are various advantages of using paracetamol to close the PDA in newborns. It is an effective alternative to more traditional therapies like indomethacin and ibuprofen. For preterm newborns, it is safer because it has no appreciable effect on the gastrointestinal system or renal function. A successful PDA closure improves the baby's overall health outcomes by lowering the likelihood of problems, including heart failure, pulmonary bleeding, and chronic lung disease[19].

The present work observed that the rate of PDA non-closure was significantly higher in neonates who were delivered with a gestational age of < 30 weeks, birth weight of < 1500 g, whose mothers didn't receive antenatal steroids, or had hypertension, neonates with moderate PDA size, and those who received two sessions of paracetamol therapy (P<0.05). Similarly, Vaidya et al. observed that infants with failed PDA closure were more likely to be lower gestational age, lower birth weight (P<0.05), while no relation was observed between the closure and the PDA size, antenatal steroid and the maternal co-morbidities (P>0.05)[20].

Moreover, it had been observed that most published studies from the eastern hemisphere, enrolling larger gestational age infants with a mean gestational age > 30 weeks, in which the closure rate was significantly increased with the increment of gestational age, as approved in Kumar et al.'s study[21] and Menna et al.'s study [22]. On the other hand, larger birth weight infants ranged between 1000–1500 g or more, had a higher chance of closure, meaning the presence of a significant association between the closure rate and the birth weight, as reported in Al-Lawama et al study[23] and El-Mashad et al study[24]. In comparison to other studies, different results were observed in Depala et al study, in which they observed that gestational age was significantly lower in infants with failed PDA closure (P=0.017) and infants delivered vaginally were significantly less likely to experience spontaneous PDA closure, while no association observed with birth weight, neither with PDA size (P>0.05)[25].

The current study reported that there was no significant association between the PDA size and the number of paracetamol sessions (P= 0.262). This finding was in agreement with that published in Vaidya et al study, in which the closure of PDA was not related to the sessions of paracetamol drug used (P>0.05)[20]. The differences among the above studies might be related to the differences in study design and sample size. Also, a combination of gestational age, oxygenation status, prostaglandin regulation, heart defects, medications, genetics, and environmental influences contributes to the variability among the above studies. In fact, premature neonates have a reduced rate of spontaneous closure because their circulatory systems and lungs are still developing. Lower amounts of prostaglandin breakdown in preterm newborns may cause a delayed or missing closure[26]. Moreover, these infants typically have an open ductus arteriosus due to a lack of physiological cues for closure (such as prostaglandin metabolism and oxygen levels). Also, the lungs may not have fully matured in low-birth-weight babies, which could result in inadequate oxygen exchange, which precludes spontaneous closure[27].

Most of the research on the mechanism of action of paracetamol is still ongoing, like cyclooxygenase inhibitors. Paracetamol first causes smooth muscle constriction and lumen narrowing by blocking the synthesis of prostaglandin. Platelet aggregation is essential for the formation of a thrombus that occludes the ductal lumen in the latter stages of ductal closure. This part of the closure process may benefit from paracetamol's reduced anti-platelet activity in comparison to cyclooxygenase inhibitors[28].

In conclusions, the present study shows that paracetamol is effective in closure of PDA in preterm neonates of <34 weeks of gestation. Some neonates required two courses of the trial drug for closure. Paracetamol is a safer drug than the other NSAIDs that are used in the closure of PDA because it has fewer side effects on the gastrointestinal and renal systems.

Conflict of interest: The authors have no conflicts of interest to declare.

Author's contribution: Author 2 conceived the idea and designed the study. Author 1 conducted the experiments and collected the data. Data analysis was performed by authors 1 and 2. The manuscript was written by author 1 and revised by author 2. All authors read and approved the final manuscript.

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