COMPARISON OF INTRAVENOUS VERSUS ORAL PARACETAMOL IN PRETERM NEONATES WITH PATENT DUCTUS ARTERIOSUS

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ABSTRACT

Background: Patent ductus arteriosus is one of the most critical complications in preterm babies, which can affect survival and long-term outcomes if not properly treated.

Objective: The aim of the study was to compare the efficacy of oral route versus intravenous paracetamol in promoting ductal closure in preterm neonates.

Materials And Methods: This cross-sectional study was carried out in the Pediatrics Department of the Lady Reading Hospital, Peshawar, over a period of six months after approval of the synopsis A total of 154 preterm neonates were enrolled using a consecutive sampling method , with 77 patients in the IV group (Group A) and 77 in the oral group (Group B). The allocation was governed by the availability of the drug and preference of treating physician .In case of unavailability of paracetamol, ibuprofen was kept as an alternative option ensuring continuity of care without compromising ethical or treatment standards. Baseline demographic details were recorded, and at the completion of treatment, the outcome in terms of PDA closure was noted. Data analysis was done using SPSS latest version, with the chi-square test applied for comparing efficacy of paracetamol between groups.

Results: Oral paracetamol achieved higher PDA closure rates than intravenous therapy (80.5% vs. 67.5%). Closure was significantly greater in infants aged 32–34 weeks ($p = 0.02$) and in those with parents having secondary education ($p = 0.03$). A non-significant trend toward better outcomes was observed in females ($p = 0.07$), while socioeconomic status ($p = 0.91$) and neonatal weight ($p = 0.88$) had no effect.

Conclusion: Oral paracetamol was more effective than intravenous paracetamol in promoting PDA closure in specific subgroups, particularly in neonates aged 32–34 weeks and those with parents having secondary education. This is essential as both educational and socioeconomic status are relevant as they can indirectly influence neonatal outcomes through factors such as timely access to treatment, antenatal care and availability of medications.

Keywords: Efficacy, Paracetamol, PDA, Echocardiography

INTRODUCTION

The ductus arteriosus is a vital fetal vascular shunt connecting the pulmonary artery with aorta, enabling blood to trespass the dysfunctional fetal lungs and maintain effective prenatal circulation.[1] Following birth, as the newborn transitions to postnatal life, this duct normally undergoes functional closure within 24 to 72 hours in healthy term infants.

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This closure is driven primarily by a rise in postnatal oxygen levels, increased pulmonary blood flow, and a reduction in circulating prostaglandin E_2 levels. The decrease in prostaglandins removes their vasodilatory influence, allowing the duct to constrict and eventually close.
However, in certain cases, particularly in preterm infants this closure fails, leading to a condition referred as PDA. The incidence is notably high in low birth weight individuals, with rates approaching 50% in some reports.[2] Persistent PDA in this vulnerable population can have serious consequences, including respiratory distress requiring prolonged ventilator support, pulmonary hemorrhage, necrotizing enterocolitis, renal dysfunction, intraventricular hemorrhage, cerebral palsy, periventricular leukomalacia, and increased mortality.[3]
Multiple therapeutic options are available for PDA management, including pharmacological closure. Nonsteroidal anti-inflammatory drugs (NSAIDs) such as ibuprofen, acetaminophen and indomethacin are widely used but may be associated with gastrointestinal bleeding, renal

impairment, and other adverse effects.[4] In recent years, paracetamol (acetaminophen) has emerged as a promising alternative due to its favorable safety profile and potential efficacy in inhibiting prostaglandin synthesis, possibly via selective COX-3 inhibition.[4] The clinical literature presents mixed findings regarding the relative efficacy of routes of NSAIDS in PDA closure. [5] Thus, the lack of clear benefit from available modalities, coupled with the potential for harm, has prompted many centers to adopt conservative or expectant management of the PDA while awaiting newer strategies that could offer improved efficacy and safety .[6]While several studies report comparable success rates between paracetamol and ibuprofen, others highlight differences in closure rates depending on the route of administration. [7]Furthermore, variations in clinical practice, timing of intervention, and patient characteristics remain sources of heterogeneity in reported outcomes. [8]

MATERIALS AND METHODS

This cross-sectional study was carried out in the Department of Pediatrics at the Lady Reading Hospital (LRH), Peshawar, over a duration of six months following approval of the synopsis dated 11th February 2025 by CPSP Ref No REU/PED-2022-022-7226.The sample size of 154 was calculated via the WHO sample size calculator, with a 5% level of significance and 80% power, based on an expected efficacy of 70% for intravenous paracetamol compared to 88% for oral paracetamol in preterm babies with patent ductus arteriosus (PDA). [5]Achieving higher power (90%) would require a substantially larger sample, which was not feasible given the limited number of eligible preterm neonates and ethical considerations of involving this vulnerable population. Therefore, 80% power was considered an appropriate and justified choice for this study. The estimated sample size was 154 neonates with allocation 1:1 being statistical efficiency and reflective of appropriate clinical physician judgment and patient condition restricting RCT and based on this consecutive sampling was employed.PDA was diagnosed based on echocardiographic findings, which included a ductal diameter of ≥1.5 mm, a left atrium-to-aortic root (LA:Ao) ratio of ≥1.5, and/or demonstration of left-to-right shunting with end-diastolic flow reversal in the aorta[7].Paracetamol was administered either intravenously or orally at a dose of 15 mg/kg every 6 hours. Follow-up echocardiographic assessments were performed at 48-hour intervals, and in cases where PDA remained patent, the treatment course was extended for a maximum duration of 6 days. Inclusion criteria were preterm neonates with gestational age in a range of 28 weeks to 36 weeks + 6 days, aged 1–7 days, of both genders, diagnosed with PDA as per the operational definition. Exclusion criteria did include individuals having previous treatment with ibuprofen, indomethacin, or surgical ligation for PDA; history of major congenital heart disease, infection at enrollment, severe intraventricular hemorrhage (Grade 3 or 4), urine output <1 ml/kg/hr in the preceding 24 hours, liver dysfunction (direct hyperbilirubinemia or ALT > 60 IU), bleeding diathesis or thrombocytopenia, and necrotizing enterocolitis (Bell stage 2 or 3). Eligible patients were recruited after obtaining informed consent from parents. Baseline demographics, including age, gender, weight, residential status, parents' education, and socioeconomic status, were recorded at study entry as they could affect the outcomes through treatment compliance and care seeking behavior. Group A consisted of neonates receiving intravenous paracetamol, while Group B comprised those treated with oral paracetamol; enrollment in each group continued until 77 patients were included. Upon completion of treatment, outcomes were assessed and documented as successful or unsuccessful PDA closure was assessed by echocardiography. Data analysis was done using SPSS latest version 22. Qualitative variables (gender, residential status, parents' education, family socioeconomic status, and efficacy) were expressed as frequencies and percentages, while quantitative variables (age and weight) were presented as mean ± standard deviation. The chi-square test was applied for comparing the efficacy between the both groups, with $p \leq 0.05$ as significant. Efficacy was further stratified by age, gender, weight, residential status, parents' education, and socioeconomic status, with post-stratification chi-square analysis applied at the same significance threshold.

RESULTS

Baseline demographic as well as clinical variables were largely comparable between the Oral and Intravenous (I/V) treatment groups. The mean age and weight were comparable with non-significant p-values (age: $p = 0.339$; weight: $p = 0.895$), indicating appropriate group matching. A borderline difference was noted in gender distribution ($p = 0.051$), with males predominating in the Oral group (63.6%) and females more prevalent in the I/V group (51.9%). Although this difference did not meet the conventional threshold for statistical significance, it approaches significance and

may represent a potential confounding factor in subsequent analyses. No statistically significant differences were observed in education level, family socioeconomic status, or the initial status of the “closure” outcome variable (all p > 0.05), further supporting baseline comparability between the study arms.

Table-1: Patients characteristics in relation to Study Groups

		Group		p-value
		Oral	I/V	
Gestational Age		32.14±1.67	31.88±1.69	**0.339**
Weight at birth		1.50±0.36	1.51±0.37	**0.895**
Gender	**Male**	49(63.6%)	37(48.1%)	**0.051[(c)]**
	Female	28(36.4%)	40(51.9%)	
Education	**Primary**	12(15.6%)	18(23.4%)	**0.327[(c)]**
	Secondary	15(19.5%)	15(19.5%)	
	Higher	11(14.3%)	5(6.5%)	
	Un-Educated	39(50.6%)	39(50.6%)	
Family Status	**Poor**	42(54.5%)	40(51.9%)	**0.942[(c)]**
	Middle	27(35.1%)	29(37.7%)	
	Rich	8(10.4%)	8(10.4%)	
Closure	**Not Closed**	15(19.5%)	25(32.5%)	**0.066[(c)]**
	Closed	62(80.5%)	52(67.5%)	

Note: (C) Chi Square test, (F): Fisher exact test, I/V: Intravenous

Baseline demographic as well as clinical variables were largely comparable between the Oral and Intravenous (I/V) treatment groups. The mean age and weight were comparable with non-significant p-values (age: p = 0.339; weight: p = 0.895), indicating appropriate group matching.A borderline difference was noted in gender distribution (p = 0.051), with males predominating in the Oral group (63.6%) and females more prevalent in the I/V group (51.9%). Although this difference did not meet the conventional threshold for statistical significance, it approaches significance and may represent a potential confounding factor in subsequent analyses. No statistically significant differences were observed in education level, family socioeconomic status, or the initial status of the “closure” outcome variable (all p > 0.05), further supporting baseline comparability between the study arms. The oral vs IV closure rates were 80.5 vs 67.7 %with an RR of 1.19 and ARR of 13%.

Table-2: Efficacy in treatment Groups stratified in relation to Patients characteristics

Variables	Category	Closure	Group		p-value
			Oral	I/V	
Age	**29-31**	**Not Closed**	5(19.2%)	7(24.1%)	**0.660[(c)]**
		Closed	21(80.8)	22(75.9%)_	
	32-34	**Not Closed**	10(19.6%)	18(37.5%)	**0.048[(c)]**
		Closed	41(80.4%)	30(62.5%)	
Gender	**Male**	**Not Closed**	12(24.5%)	13(35.1%)	**0.282[(c)]**

		Closed	37(75.5%)	24(64.9%)	
	Female	**Not Closed**	3(10.7%)	12(30%)	**0.059(c)**
		Closed	25(89.3%)	28(70%)	
Education	**Primary**	**Not Closed**	0(0%)	3(16.7%)	**0.255(f)**
		Closed	12(100%)	15(83.3%)	
	Secondary	**Not Closed**	0(0%)	7(46.7%)	**0.006(f)**
		Closed	15(100%)	8(53.3%)	
	Higher	**Not Closed**	2(18.2%)	2(40%)	**0.547(f)**
		Closed	9(81.8%)	3(60%)	
	Un-Educated	**Not Closed**	13(33.3%)	13(33.3%)	**-**
		Closed	26(66.7%)	26(66.7%)	
Family Status	**Poor**	**Not Closed**	6(14.3%)	11(27.5%)	**0.140(c)**
		Closed	36(85.7%)	29(72.5%)	
	Middle	**Not Closed**	7(25.9%)	8(27.6%)	**0.889(c)**
		Closed	20(74.1%)	21(72.4%)	
	Rich	**Not Closed**	2(25%)	6(75%)	**0.132(f)**
		Closed	6(75%)	2(25%)	
Weight of Neonate	**<1**	**Not Closed**	0(0%)	1(12.5%)	**0.444(f)**
		Closed	10(100%)	7(87.5%)	
	1.1-1.5	**Not Closed**	7(20%)	12(32.4%)	**0.232(c)**
		Closed	28(80%)	25(67.6%)	
	1.6-2.0	**Not Closed**	8(25%)	12(37.5%)	**0.281(c)**
		Closed	24(75%)	20(62.5%)	

Note: (C) Chi Square test, (F): Fisher exact test

Efficacy analyses stratified by patient characteristics revealed specific subgroups in which the oral treatment demonstrated superior outcomes.In the 32–34-week age group, the closure rate was significantly higher in the Oral group (80.4%) compared to the I/V group (62.5%), with a p-value of 0.048, indicating greater efficacy of the oral route in older neonates within the cohort. No significant differences were observed in the 29–31-week subgroup (p = 0.660).

Gender-stratified analysis did not reveal statistically significant differences for males (p = 0.282) or females (p = 0.059). However, the latter approached significance, with closure rates of 89.3% in the Oral group versus 70% in the I/V group, suggesting a possible, though not statistically confirmed, advantage of oral therapy among female patients.

In patients with secondary education, the Oral treatment achieved a 100% closure rate compared to 53.3% in the I/V group, a statistically significant difference (p = 0.006) whereas no significant differences were seen among patients with primary education, higher education, or those without formal education, with identical closure rates (66.7%) in both groups for the uneducated subgroup.

Family socioeconomic status did not significantly influence treatment efficacy, with no differences observed between the poor, middle, and rich categories (all p > 0.05). Its important because it affects the access to health care and affordability of treatment.

Similarly, neonatal weight—whether <1 kg, 1.1–1.5 kg, or 1.6–2.0 kg—did not affect comparative treatment outcomes, with closure rates remaining statistically similar between the two treatment modalities across all categories.

DISCUSSION

The role of paracetamol in PDA management has gained considerable attention since Hammerman et al. first reported successful ductal closure in premature infants treated with the drug. [7]Acetaminophen (Paracetamol), an acetanilide derivative with analgesic and antipyretic properties, is now being widely used as an alternative option for the pharmacological treatment of PDA. Several recent randomized controlled trials (RCTs) and a meta-analysis have demonstrated that its efficacy in achieving ductal closure is comparable to indomethacin and ibuprofen, while it may also be associated with a lower risk of adverse effects.[9]

In the present study, we did compare the efficacy of oral versus intravenous paracetamol for the closure of PDA in preterm babies. PDA closure was achieved in 80.5% of patients receiving oral paracetamol compared with 67.5% in those treated with the intravenous formulation. It may due to slower absorption and sustained level of drug In contrast to intravenous route. Similarly, in a study by Gover et al., the rate of ductal closure was notably more in the oral paracetamol group compared to the intravenous group (79% vs. 40%), consistent with the findings of our study. [10]In another study, Sancak et al. evaluated the efficacy of oral versus intravenous paracetamol for the closure of PDA in cases of very low birth weight infants and reported that the oral formulation was associated with a higher rate of ductal closure compared to the intravenous route.[11]

Compared with NSAIDs, paracetamol demonstrates comparable efficacy and a better safety profile for PDA closure in preterm infants. Mechanistically, it may offer advantages in NSAID-refractory cases due to its different site of action within the prostaglandin synthesis pathway. In a study of 160 infants with gestational ages below 34 weeks, Deng et al. reported ductal closure in 81.2% of those treated with standard-dose paracetamol compared with 78.8% in the ibuprofen group, supporting its role as an effective alternative.[3]

The accumulating evidence suggests that paracetamol,whether given orally or intravenously achieves closure rates comparable to, and in some cases exceeding, those of NSAIDs, with a superior safety profile. However, variability in study outcomes, particularly regarding the influence of administration route, underscores the need for further well-designed randomized controlled trials to establish optimal treatment protocols. Our study adds to this body of knowledge by directly comparing oral and intravenous administration and examining patient-related factors that may predict treatment success.[12]

This study has certain limitations. Firstly, it was done in only one tertiary care hospital, which may hamper the generalization of the findings to other populations or healthcare settings. Second, the sample size was small restricting the statistical power for detecting the subtle differences between groups. Third, only short-term outcomes were assessed; long-term follow-up regarding sustained ductal closure, neurodevelopmental outcomes, and safety was not evaluated. Finally, subgroup analyses (such as the effect of parental education and gender) were based on relatively small numbers and should be interpreted with caution.

Future multicenter randomized controlled trials with larger sample sizes are need of the day to confirm the comparative efficacy of oral versus intravenous paracetamol. Long-term follow-up studies should evaluate neurodevelopment outcomes and safety. Further research should also explore patient-specific predictors, such as gender and socioeconomic factors, to guide individualized treatment.

CONCLUSION

Oral paracetamol was more effective than IV paracetamol in promoting PDA closure, particularly in neonates aged 32–34 weeks and those with parents having secondary education.

DECLARATIONS

Authors contributions:

Dr. Maira Khalid conceptualized the study, contributed to the study design, data interpretation, and manuscript drafting. All authors participated in data collection, analysis, and critical review of the final manuscript. All authors have read and approved the final version of the manuscript.

Conflicts of Interests: The authors declare that there are no conflicts of interest regarding the publication of this paper.

Funding: This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Acknowledgements: The authors express their sincere gratitude to the staff and participants who contributed to this study. Special thanks to the Department of Paeds Lady Reading Hospital Peshawar

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