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Original Article

Effect and Outcome of Paracetamol on PDA in Term and Preterm Sick Newborn in NICU of a Tertiary Care Hospital

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ABSTRACT

Background: *Patent Ductus Arteriosus (PDA) is a common condition in premature newborn, which often leads to significant morbidity. Traditional treatment, such as COX inhibitors (ibuprofen, indomethacin), represent risks such as necrotizing enterocolitis and kidney damage. Paracetamol, an alternative that inhibits prostaglandin synthesis, has proved to be a promising treatment for the closure of PDA in newborns, but its efficacy in premature versus the term infants remains suspicious.* ***Methods & Materials:*** *This retrospective study evaluated the effect of paracetamol on PDAD closure in 35 neonates in a NICU from January 2023 to December 2023. Inclusion criteria were neonates diagnosed with PAD and treated with paracetamol. PDA size was assessed before and after treatment using echocardiography, with primary outcomes being PDA reduction and secondary outcomes including closure rates and adverse events.* ***Results:*** *Paracetamol significantly reduced PDA size in both term (mean reduction: 2.5 mm) and preterm infants (mean reduction: 1.38 mm). The PDA closure was achieved in 45.7% of cases, with a partial closure of 14.3%. Regression analysis confirmed the positive impact of paracetamol, especially in infants (p <0.001). Premature infants showed less effect of treatment (p = 0.022).* ***Conclusion:*** *Paracetamol is an effective alternative for managing PDA, with term neonates showing greater PDA reduction than preterm infants. These findings suggest that paracetamol could be a promising option for PDA management.*

Keywords: *Premature newborns, Indomethacin, Echocardiography, Adverse events*

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INTRODUCTION

The intricate interplay between congenital heart disease (CHD) and systematic hemodynamics underscores the critical need to examine its impact on oxygen perfusion, cardiac output, and vascular integrity, particularly in vulnerable neonatal populations [1]. Severe congenital heart disease (CHDs) in preterm infants, particularly those with birth weights below 1500 g, exhibit alarmingly high mortality rates (44-55%), compound by multifactorial vulnerabilities such as gestational immaturity, extracardiac malformations, and genetic syndromes [2]. Congenital heart disease (CHD) affects 7.8 per 1000 live births in Bangladesh, contributing significantly to neonatal mortality, which ranks as the fourth leading cause of newborn deaths, while advancements in early detection and treatment in developed nations have reduced CHD-related mortality from 80% to 20% [3]. Paracetamol, by inhibiting prostaglandin synthesis, offers a promising alternative for closing hemodynamically significant patent ductus arteriosus (hsPDA) in preterm neonates, with studies reporting a 70% success rate while minimizing complications like NEC, kidney failure, and bleeding [4,5]. Hemodynamically significant patent ductus arteriosus (PDA) affects preterm infants, with COX inhibitors achieving a 70% success rate but posing risks like kidney failure, while paracetamol offers a safer alternative by inhibiting prostaglandin synthesis for ductal closer [6]. Hemodynamically significant PDA remains a major concern in preterm neonates, often complicating respiratory distress syndrome and increasing the risk of severe morbidity. The persistence of PDA is primarily mediated by prostaglandins, synthesized through prostaglandin H2 synthetase (PGHS), necessitating pharmacological intervention for closure. Traditional cyclooxygenase (COX) inhibitors like ibuprofen and indomethacin have shown a closure rate of approximately 70%, yet their association with complications such as necrotizing enterocolitis, renal impairment, and gastrointestinal bleeding limits their use in critically ill neonates [6,7]. Recent studies indicate that paracetamol, acting through inhibition of the peroxidase component of PGHS, provides a promising alternative with a potentially safer

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profile. Although paracetamol is widely used in pediatric medicine, its role in PDA closure remains underexplored, with varying outcomes across different clinical settings. While some trials suggest comparable efficacy between paracetamol and COX inhibitors, inconsistencies in optimal dosing strategies and treatment duration highlight the need for further research [8-10]. Additionally, disparities in healthcare access, particularly in resource-limited settings, there is a need for a more cost-effective and safe treatment such as oral medications like paracetamol or ibuprofen, non-invasive interventions like oxygen therapy, and supportive care, all of which can offer effective management of conditions like PDA and ASD while minimizng financial and logistic barriers [13, 14]. In pediatric care, an individualized approach is essential, where efficacy and safety are measured in drug therapy to minimize side effects [15]. In light of these considerations, this study aimed to evaluate the efficacy and outcome of paracetamol in the treatment of patent ductus arteriosus (PDA) in premature infants. These findings underscore paracetamol's therapeutic efficacy in facilitating PDA closure, demonstrating a pronounced hemodynamic response in term neonates while highlighting the necessity for optimized pharmacological strategies in preterm cohort.

METHODS & MATERIALS

This retrospective obserational study aims to assess the effect and outcome of paracetamol on the closure of patent ductus arteriosus (PDA) in both term and preterm sick neonates in the Neonatal Intensive Care Unit (NICU) of a tertiary care hospital. Data were collected from the medical records of neonates diagnosed with clinically significant PDA and treated with paracetamol between January 2020 and December 2023. The inclusion criteria were neonates diagnosed with PDA (either term or preterm) and treated with paracetamol, with complete clinical data available for analysis. Exclusion criterai included neonates with contraindications to paracetamol (e.g., liver dysfunction), those with incomplete clinical data, and neonates who did not receive paracetamol treatment. A total of 35 neonates (19 terms, 13 preterm, and 3 near-term) were included, with sampling done via convenience sampling from the NICU admissions during the study period. The primary outcome was the reduction in PDA size, measured by echocardiography before and after paracetamol treatment. Secondary outcomes included PDA closure rates and adverse events. Descriptive statistics weree used for demographic and clinical characteristics, while comparisons of mean and median PDA reduction between term and preterm groups were made using independent t-tests. Linear regression analysis was performed to quantify the effect of paracetamol on PDA reduction, with p-values < 0.05 considered statistically significant.

RESULTS

The basic characteristics of the study population presents the distribution of the study population based on basic demographic characteristics. The mean age of the participants is 6.93 days, with minimum age 3 days and the maximum being 17 days. This distribution suggests that the population includes both young children and young adults. Among 35 participants, 19 (54.3%) neonates are male, and 16 (45.7%) are female, indicating a predominance of males in the study cohort. [Table I]

Table I: Distribution of study population based on the basic characteristics (*n*=35)

Age (in days)	(n, %)
Minimum	3
Maximum	17
Mean ± SD	6.93 ± 3.882
Gender	
Male	19, 54.3
Female	16, 45.7

The distribution of these defects within the sample population is presented in the Table 2, All patients in this study were clinically diagnosed with congenital heart disease (CHD), and each case was carefully categorized based on the specific type of CHD. All neonates had ASD and PDA. Moreover, study population also had one or more associated medical complications such as jaundice (8,22.9 %), intrauterine growth restriction - AGA (18, 51.4%), PNA (7, 20%), PPHN (1, 2.9%), IDM (11, 31.4%), TTN (11, 31.4%), RDS (5, 14.3%), EONS (13, 37.1%), NNJ (8, 22.9%), MAS (4, 11.4%), HIE (2, 5.7%), LGA (3, 8.6%). [Table II]

Table – II: Distribution of Study Population Based on Clinical History (*n*=35)

Population Overview	(n, %)
Gestational Age	
Term	19, 54.3%
Pre-term	13, 37.1.0%
Near Term	3, 8.6%
Associated Medical Condition	
AGA (Appropriate for Gestational Age)	18, 51.4%
PNA (Perinatal Asphyxia)	7, 20%
PPHN (Persistent Pulmonary Hypertension of Newborn0	1, 2.9%
IDM (Infant of Diabetic Mother	11, 31.4%
TTN (Transient Tachypnea of Newborn)	11, 31.4%
RDS (Respiratory Distress Syndrome)	5, 14.3%
EONS (Early Onset of Neonatal Sepsis)	13, 37.1%
NNJ (Neonatal Jaundice)	8, 22.9%
MAS (Meconium Aspiration Syndrome)	4, 11.4%
HIE (Hypoxic-Ischemic Encephalopath)	2, 5.7%
LGA (Large for Gestational Age)	3, 8.6%

In the current study all neonates had PDA and ASD. For PDA, the mean value is 1.75 with a standard deviation of 1.19. In contrast, ASD has a significantly higher mean of 3.09 with a standard deviation of 1.12 [Table III].

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Table III: Pattern of Congenital Heart Disease Among the Study Population (*n*=35)

Pattern of CHD	Mean ± Std	Minimum	Maximum
PDA	1.7477 ± 1.19	.50	6.00
ASD	3.09 ± 1.12	0	6

The table outlines the treatment details for a sample of 35 study population. Of them, 30 (85.7%) samples received treatment, while 5 (14.3%) did not. The types of treatments provided include O2 inhalation was administered to 29 (82.9%) samples. Other treatments include Napa drop, given to 3 (8.6%), Injection Napa, provided to 13 (37.1%) neonates, Syrup Ibuprofen, used by 1 (2.9%) patients and Tablet Vigorex, also used by 1 (2.9%). [Table IV]

Table – IV: Treatment Pattern in Congenital Heart Disease (CHD) Among the Study Population. (*n*=35)

Treatment	(n, %)
Treatment - Provided	30, 85.7%
Treatment – Not Provided	5, 14.3%
Treatment Type	
O2 Inhalation	29, 82.9%
Drop Napa	3, 8.6%
Injection Napa	13, 37.1%
Syrup Ibuprofen	1, 2.9%
Tablet Vigorex	1, 2.9%

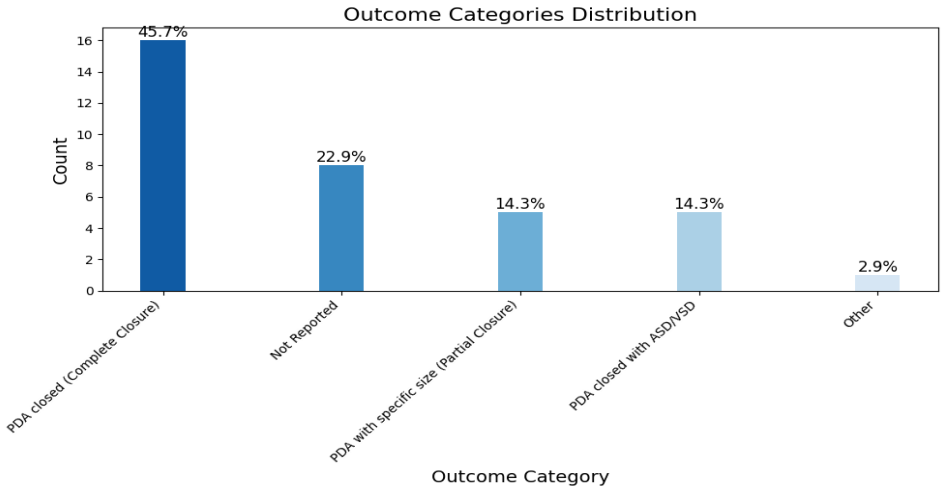

Figure – 1: Distribution of Outcome Categories for PDA Cases

The bar chart illustrates the distribution of outcome categories for PDA cases, with percentages indicating their proportions. The largest category, "PDA Closed" (Complete Closure), accounts for 45.7% of cases, representing nearly half of the patients achieving the desired outcomes. The second-largest group, "Not Reported" constitutes 22.9%, highlighting gaps in data reporting. "PDA with Specific Size (Partial Closure)" and "PDA Closed with ASD/VSD" and each make up 14.3% of cases, reflecting the variability in outcomes, including partial closure and concurrent cardiac defects like ASD or VSD. The "Other" category is the smallest representing only 2.9%, likely encompassing rare or miscellaneous outcomes. Overall, the chart underscores the importance of achieving complete PDA closure while addressing reporting gaps and the complexities of managing co-morbid conditions. **[Figure 1]**

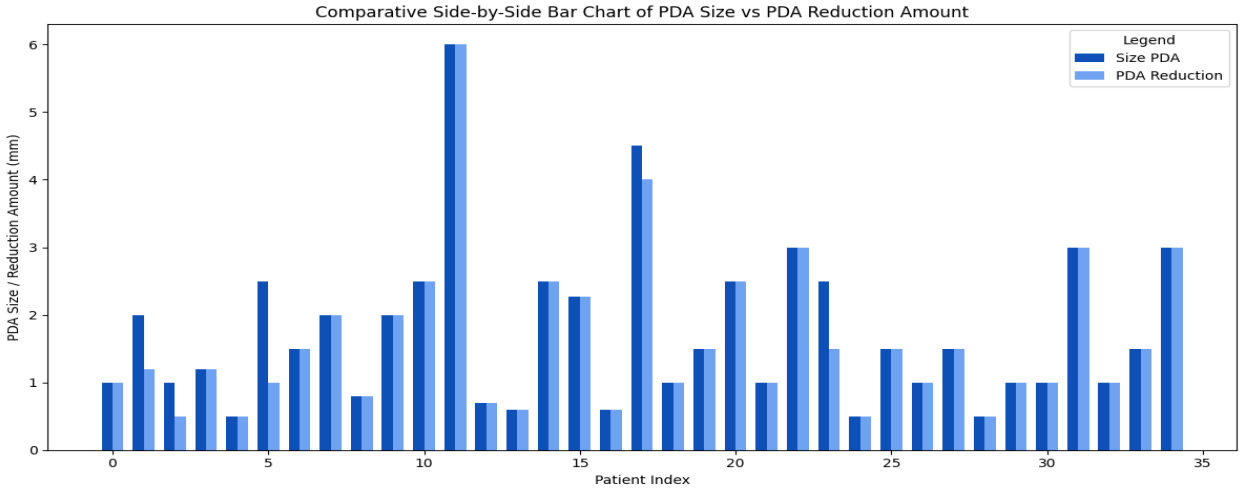

Figure – 2: Comparative Bar Chart of PDA Size and Reduction Amount

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The graph presents a comparative analysis of PDA size and reduction amount for 35 CHD patients. Each patients have two bars: one for initial PDA size and the other for the reduction amount, both measured in millimeters. The largest PDA size, observed for ten patients, is approximately 6mm, with an equal reduction of 6mm, indicating complete closure. Thirty and thirty-five patients also show PDA sizes of around 3mm, with nearly complete reductions. Conversely, some patients, such as Patient 5, have a PDA size of about 2.5mm but only a reduction of approximately 1mm, indicating partial closure. Similarly, patient 20 has a PDA size of roughly 2.8mm but a reduction of just 1.5mm. The graph highlights that PDA sizes vary from less than 1 mm to 6 mm across patients, while reductions span from negligible amounts to complete closure. **[Figure 2]**

The linear regression model's goal is to analyze the effect and impact of paracetamol treatment on PDA reduction by quantifying the relationship between the predictor(treatment) and outcome (PDA reduction). The intercept indicates a baseline PDA reduction of 1.0195 mm (t=4.263, p<0.001), with a 96% confidence interval (CI) of [0.571, 1.468], suggesting a consistent baseline effect. Paracetamol treatment enhances PDA reduction by 1.3243 mm (t = 4.060, p < 0.001), with a 96% CI of [0.661, 1.988], confirming itis significant positive impact. These results highlight paracetamol's efficacy and high t-value and observed confidence intervals suggest the precision and reliability of these estimates. [Table V]

Table – V: Impact of Paracetamol Treatment on PDA Reduction: Regression Analysis Results (*n*=35)

Group	Predictor	Coefficient(coef)	t-value	p-value	95% CI (Lower, Upper)
Term Babies	Paracetamol Treatment	2.500	5.590	0.00	[1.488, 3.512]
Preterm Babies	Paracetamol Treatment	1.3750	4.371	0.02	[0.374, 2.376]

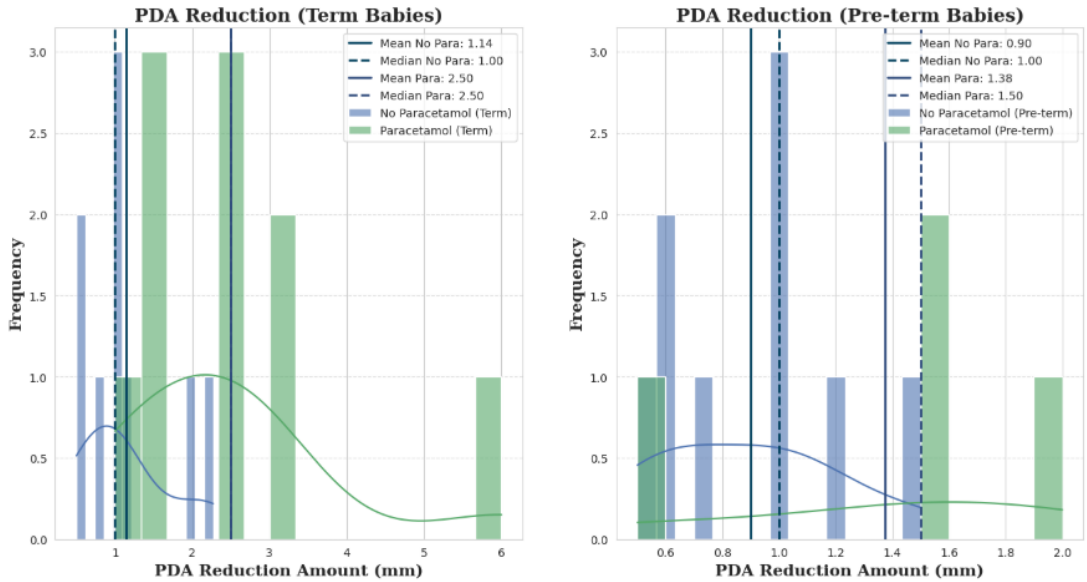

Figure – 3: Effect of Paracetamol on PDA: Histogram with statistical comparison of Mean and Median

The histogram follows the effect of Paracetamol and its outcome on PDA reduction in Term and Pre-term infants, which shows a significant difference between the two groups. For term babies, the mean PDA reduction is 2.50 mm with paracetamol versus 1.14 mm without (mean difference 1.36 mm; p < 0.001), while for preterm babies, the mean reduction is 1.38 mm with paracetamol compared to 0.90 mm without (mean difference 0.48 mm; p=0.022). The overlap in the histogram reflects a smaller treatment effect in preterm babies, consistent with higher p-value. [Figure 3]

DISCUSSION

In the present study, the demographic characteristics ((n=224)) showed a male predominant (52.23%), with the majority (37.94%) of patients presenting between 1 and 12 months of age, while most prevalent CHD lesions were VSD (29.01%), ASD (14.73%), and PDA (12.5%) [7]. Even, the study population in our study showed 54.3% males, while focuses exclusively on ASD and PDA (100%) that additionally integrated with associated medical conditions like Jaundice (51.4% vs 43.3%) and EONS (37.1% vs 37.1%) To give an example, in the study of Gupta RK et al. (n=100), VSD (32%) was the most common lesion followed by ASD (16%) and PDA (12%), with major complications including growth failure (27%) and heart failure (21%) [8]. To be more precise, our studdy (n=35), ASD and PDA both had 100% occurence, with PDA showing a mean of 1.75 ± 1.19, and associated medical conditions such as jaundice (51.4%) and intrauterine growth restriction (31.4%). In addition, the study of Isayama et al. showed that among preterm infants (37.1%) and Drop Napa (8.6%), highlighting its significant role in PDA management

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compared to varied international treatment rates [9]. In particular, the study of preterm babies born before 32-week gestational age portrayed that Paracetamol (IV: 45, Oral: 42) treated PDA in 87 preterm neonates (<32 weeks), with closure in 31 (43.66%), size reduction in 40 (56.34%), and failure in 16 (18.39%), showing no significant difference between IV (82.22%) and oral (80.95%) groups (p=0.94) [10]. Subsequently, our study uniquely quantifies paracetamol's greated PDA reduction in term (2.5 mm, $p < 0.001$) vs. Preterm infants (1.388 mm, p=0.022), highlights precise PDA size reduction (1.32 mm, $p < 0.001$), identifies outcome variability (45.7% complete, 14.3% partial, 22.9% unreported), and details comorbidities and treatment patterns. The study of Höck et al. found that paracetamol treatment resulted in a significantly higher PDA closure rate (86.4% vs. 61.8%, p<0.001) and improved outcomes, with lower ibuprofen use in the paracetamol group and a mean treatment duration 4.97 days [11]. On top of that, our study confirming paracetamol's positive impact on PDA reduction (mean difference 1.36 mm for term babies, $p < 0.001$). Also, the study of Dani et al. and Schindler et al. evaluated primary and secondary outcomes for PDA closure and constriction with paracetamol (n=55) versus ibuprofen (n=55), showing that paracetamol was less effective in closing hsPDAD (52% vs. 78%, p=0.026) but had a similary constriction rate (81% vs 90%, p=0.202) [12]. Both Schindler et al. and Iacobelli et al. Investigate paracetamol for treating PDA in term and preterm infants, with showing 59% and 68% reduction rate in PDA refractory cases [13, 16]. In this study, 35 infants with PDA received treatment, with 30 (85.7%) receiving various treatments, incluing O2 inhalation (82.9%), and paracetamol significantly reduced PDDA size by 1.32 mm in both term (2.50 mm) and preterm (1.38 mm) infants. Nonetheless, our study (n=35) revealed a 45.7% PDA closure with paracetamol, with a mean reduction of 2.5 mm in term babies (p<0.001) and 1.38 mm in preterm (p=0.022).

CONCLUSION

The study demonstrated that paracetamol significantly enhances PDA closure, with term neonates exhibiting a greater reduction in PDA size than preterm infants. The findings highlight a strong therapeutic potential for paracetamol in PDA management, with a mean reduction of 2.5 mm in term infants (p<0.001) and 1.38 mm in preterm infants (p=0.022). The observed closure rate of 45.7% underscores its effectiveness, through variability in response suggests the need for individualized treatment approaches. The regression analysis confirmed the significant impact of paracetamol, reinforcing its role as a viable alternative to ibuprofen. Treatment distribution analysis also revealed a preference for oxygen inhalation and other adjunctive therapies in managing PDA. Despite partial closure in some cases, the overall response suggests promising pharmacodynamic effects warranting further investigation.

Limitation of the Study

The study is limited by its small sample size (n=35), which may restrict the generalizability of finings to broaer populations. Additionally, the lack of control group receiving standard treatments limits comparative efficacy assessments. Further, variability in treatment response necessitates larger, multicentric trials to validate these findings and optimize therapeutic protocols.

RECOMMENDATION

Paracetamol should be considered an effective alternative for PDA management, especially in term infants, with further studies needed to optimize dosage and compare its efficacy to other treatments. Personalized treatment protocols and stanardized monitoring are essential for improving outcomes in neonates with PDA.

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