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Original Research Article

Effectiveness of Paracetamol in Treating Hemodynamically Significant Patent Ductus Arteriosus in Preterm Newborns

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Abstract:

Background: Patent ductus arteriosus (PDA) is a common condition in preterm infants, often requiring medical intervention for closure. Traditional treatments such as indomethacin and ibuprofen are associated with adverse effects, prompting the exploration of alternative therapies. Paracetamol (acetaminophen) has emerged as a potential alternative with a favorable safety profile, but its efficacy in preterm infants remains under investigation.

Aim: The aim of this study is to evaluate the efficacy of paracetamol in the management of hemodynamically significant PDA in preterm newborns, focusing on ductal closure rates, respiratory improvement, and the need for further interventions.

Methods: This prospective observational study was conducted at Jawaharlal Nehru Medical College & Hospital, enrolling 50 preterm infants diagnosed with hemodynamically significant PDA. Paracetamol (15 mg/kg iv every 6 hours) was administered for 120 hours. Clinical outcomes, including PDA closure, respiratory status, and the need for additional treatments, were monitored. Data were analyzed using SPSS version 23.0.

Results: Out of 50 infants, 35 (70%) achieved complete PDA closure after 120 hours of paracetamol therapy. Respiratory improvement was observed in 28 (56%) infants, with a reduction in oxygen requirements. The mean duration of paracetamol treatment was 4.8 ± 0.9 days, and the mean NICU stay was 14.3 ± 3.2 days. No severe adverse events were noted, though 3 (6%) infants experienced mild transient liver enzyme elevation.

Conclusion: Paracetamol was found to be an effective treatment for PDA in preterm infants, with high closure rates and a favorable safety profile compared to traditional treatments. It may serve as a viable alternative to indomethacin or surgical ligation in managing PDA.

Recommendations: Paracetamol should be considered as a first-line pharmacological treatment for PDA in preterm infants, particularly in cases where traditional treatments are contraindicated or carry a high risk of adverse effects. Further studies with larger cohorts are needed to confirm these findings and assess long-term outcomes.

Keywords: Paracetamol, Patent Ductus Arteriosus, Preterm Infants, Pharmacological Treatment, Neonatal Care..

Introduction

A frequent cardiovascular disorder in preterm newborns is called (PDA), in which the ductus arteriosus, a conduit that connects the aorta and pulmonary artery, fails to seal after delivery. This causes aberrant blood flow between the two main vessels, which can cause respiratory discomfort, severe hemodynamic instability, and a higher chance of consequences such intraventricular and pulmonary bleeding. Due to the vascular structures' immaturity, PDA is more common in preterm newborns; those born before 28 weeks of gestation have a greater frequency. In fact, studies have shown that approximately 50-70% of extremely low birth weight infants (<1000g) will have a persistent PDA that requires medical or surgical intervention for management [1]. Traditionally, PDA in preterm infants has been treated with pharmacologic agents like indomethacin or ibuprofen, both of which inhibit cyclooxygenase and prostaglandin synthesis to promote ductal closure. However, the use of these drugs is restricted in some situations due to a number of side effects, such as renal failure, gastrointestinal bleeding, and decreased platelet aggregation [2]. As a result, there has been growing interest in exploring alternative therapies with fewer side effects.

Recently, paracetamol, often known as acetaminophen, has shown promise as a substitute for treating PDA in premature infants. Mechanism of action involves inhibitions of prostaglandin E^2 synthesis and inhibitions of cyclooxygenase pathway by inhibiting peroxide activity. Recent studies have demonstrated that paracetamol may effectively close the PDA without the associated renal or gastrointestinal complications seen with other pharmacological treatments [3]. Moreover, studies have suggested that paracetamol has a lower risk of affecting platelet function and renal function, making it a more attractive option in preterm neonates, who are particularly vulnerable to these adverse effects [4]. Clinical trials have increasingly supported the use of paracetamol for PDA management. A randomized controlled trial found that paracetamol was equally effective as indomethacin in achieving ductal closure, with fewer renal complications and no significant adverse effects on long-term growth and development [5]. However, despite the encouraging results, the use of paracetamol in this context remains underutilized, with some clinicians preferring traditional treatments due to familiarity and established guidelines. The long-term effectiveness and safety of paracetamol as a first-line treatment for PDA in preterm newborns must thus be confirmed by additional research. The aim of this study is to evaluate the efficacy of paracetamol in the management of hemodynamically significant PDA in preterm newborns, focusing on ductal closure rates, respiratory improvement, and the need for further interventions.

Methodology

Study Design

This is a prospective observational study.

Study Setting

The study will be conducted at the Jawaharlal Nehru Medical College & Hospital, a tertiary care center with a neonatal intensive care unit (NICU) equipped for the management of preterm infants. This hospital provides comprehensive neonatal care, including treatment for congenital cardiac conditions, and is an ideal setting for the proposed study. The study will span from November 2023 to October 2024.

Participants

A total of 50 preterm newborns diagnosed with hemodynamically significant patent ductus arteriosus (hsPDA) will be included in the study. These infants will be selected

from the NICU of Jawaharlal Nehru Medical College & Hospital. The inclusion of a relatively small sample size ensures a manageable patient group, allowing for detailed clinical monitoring and assessment during the treatment period.

Inclusion Criteria

- Preterm infants (gestational age < 37 weeks) diagnosed with (hsPDA) on echocardiographic examination.
- Infants requiring pharmacological closure of the PDA.
- Age less than 7 days at the time of diagnosis.
- Parental or guardian informed consent was acquired for study participation.

Exclusion Criteria

- Infants with major congenital anomalies (excluding PDA).
- Infants with severe birth asphyxia or other life-threatening conditions.
- Infants with known allergies to paracetamol or contraindications to its use.
- Neonates requiring surgical ligation of PDA before starting medical treatment.
- Infants with incomplete medical records or failure to follow up during the treatment period.

Bias

To minimize bias, the study will use a systematic inclusion process and will ensure that all participants are treated according to the standard care protocol for PDA management. Both clinical and echocardiographic assessments will be performed by trained neonatologists to ensure consistency in diagnoses. Data collection will be blinded to the study's primary outcome variables, and the final analysis will be conducted by an independent statistician.

Data Collection

Data will be collected from medical records of the enrolled preterm infants, including demographic details, clinical presentations, echocardiographic findings, and treatment responses. Parameters such as gestational age, birth weight, age at diagnosis, duration of paracetamol therapy, and any adverse events will be documented. Clinical outcomes such as PDA closure rates, the need for additional treatments, and the duration of NICU stay will be recorded.

Procedure

Once informed consent is obtained, infants will be enrolled in the study and will undergo initial echocardiographic evaluation to confirm the diagnosis of hsPDA. Intravenous Paracetamol treatment (15 mg/kg every 6 hourly for 120 hrs) was initiated for all participants, with close monitoring for any adverse effects. Echocardiographic evaluation repeated every 72hrs to assess the closure of the ductus arteriosus. Infants was monitored for clinical signs of PDA, including signs of respiratory distress or cardiovascular instability. If the ductus remains open after 5 days of paracetamol treatment, alternative treatments will be considered.

Statistical Analysis

SPSS version 23.0 (IBM Corp., Armonk, NY, USA) was used to analyze the data. Frequency distributions, mean, and standard deviation are examples of descriptive statistics that was used to characterize clinical outcomes and demographic information. Fisher's exact test for categorical variables or chi-square tests was used to assess the main result, PDA closure rates. When applicable, t-tests or Mann-Whitney U tests was used to assess continuous variables, such as the length of therapy or NICU stay. The threshold for statistical relevance was $p < 0.05$.

Results

A total of 55 preterm neonates were enrolled in the study, with 50 infants completing the study protocol. The demographic characteristics of the study

participants, as well as clinical outcomes, were recorded and analyzed.

The study cohort consisted of preterm infants with a mean gestational age of 31.2 ± 2.4 weeks, and the mean birth weight was 1.25 ± 0.4 kg. Among the 50 participants, 30 (60%) were male and 20 (40%) were female. The distribution of birth weight showed that 25 infants (50%) had a birth weight of less than 1.5 kg, while 25 (50%) had a birth weight of more than 1.5 kg.

Table 1: Demographic Characteristics of Participants

Parameter	Value
Total number of infants	50
Male (%)	30 (60%)
Female (%)	20 (40%)
Mean Gestational Age (weeks)	31.2 ± 2.4
Mean Birth Weight (kg)	1.25 ± 0.4
Birth Weight < 1.5 kg (%)	25 (50%)
Birth Weight ≥ 1.5 kg (%)	25 (50%)

The primary outcome of the study was the closure of the (PDA) following treatment with paracetamol. Of the 50 infants included in the final analysis, 35 (70%) had complete closure of the PDA after 5 days of paracetamol therapy. In contrast, 15 (30%) did not achieve closure and required further interventions, such as surgical ligation or alternative pharmacological treatments.

Table 2: PDA Closure Rates Post-Treatment with Paracetamol

Outcome	Number (%)
PDA Closed (after 5 days)	35 (70%)
PDA Not Closed (requiring further treatment)	15 (30%)

The response to paracetamol therapy was monitored using clinical parameters such as respiratory stability, cardiovascular function, and the need for additional interventions. The results indicated that 28 (56%) infants showed marked improvement in respiratory function, with a significant reduction in oxygen requirements and respiratory distress signs within 48 hours of initiating paracetamol therapy.

Table 3: Clinical Response to Paracetamol Treatment

Clinical Outcome	Number (%)
Improved Respiratory Function (reduced oxygen needs)	28 (56%)
No Improvement in Respiratory Function	22 (44%)

The average duration of paracetamol treatment was 4.8 ± 0.9 days. The mean length of stay in the NICU was 14.3 ± 3.2 days, with infants who responded well to the treatment having a shorter stay compared to those who required additional interventions.

Table 4: Duration of Paracetamol Treatment and NICU Stay

Outcome	Value
Mean Duration of Paracetamol Treatment (days)	4.8 ± 0.9
Mean Length of NICU Stay (days)	14.3 ± 3.2

Chi-square tests were used to compare PDA closure rates and the improvement in respiratory function between various groups based on gestational age and birth weight. No statistically significant correlation was found between gestational age groups or birth weight categories for the primary outcome of PDA closure ($p > 0.05$). However, infants with a birth weight greater than 1.5 kg showed a higher rate of respiratory improvement (62%) compared to those with a birth weight less than 1.5 kg (48%), though this difference was not statistically correlated ($p = 0.21$).

Table 5: Comparison of PDA Closure and Respiratory Improvement by Birth Weight

Parameter	Birth Weight < 1.5 kg (n=25)	Birth Weight ≥ 1.5 kg (n=25)	p-value
PDA Closure Rate (%)	22 (88%)	13 (52%)	0.032*
Respiratory Improvement (%)	12 (48%)	15 (62%)	0.21

*Statistically significant ($p < 0.05$).

A small number of infants (3 out of 50, 6%) experienced mild adverse events related to paracetamol treatment, including transient liver enzyme elevation. These infants were closely monitored, and no permanent adverse effects were noted. No cases of severe adverse reactions, such as gastrointestinal bleeding or renal failure, were reported.

Table 6: Adverse Events During Paracetamol Treatment

Adverse Event	Number (%)
Mild Liver Enzyme Elevation	3 (6%)
No Adverse Events	47 (94%)

Discussion

The study enrolled 50 preterm infants, out of these, 35 infants (70%) showed complete closure of the (PDA) after 5 days of treatment with paracetamol, indicating that paracetamol is an effective pharmacological intervention for managing hemodynamically significant PDA in preterm newborns. However, 15 infants (30%) did not experience closure and required additional treatments, such as surgical ligation or alternative medications.

Regarding clinical outcomes, 56% of infants showed marked improvement in respiratory function, with reduced oxygen requirements and fewer signs of respiratory distress within 48 hours of starting paracetamol therapy. This suggests that paracetamol not only aids in PDA closure but also helps stabilize respiratory function, contributing to improved overall clinical management in preterm infants with PDA. The average duration of paracetamol treatment was 4.8 days, and the mean length of stay in the NICU was 14.3 days. The treatment group that responded well to paracetamol had a shorter NICU stay compared to those who needed further interventions, supporting the idea that early successful treatment of PDA may reduce the overall hospital stay for preterm infants. The statistical analysis revealed that birth weight did not significantly affect the rate of PDA closure ($p > 0.05$), though a higher proportion of infants with birth weights greater than 1.5 kg showed improvement in respiratory function. However, this difference was not statistically significant. The study also noted a low incidence of adverse events, with only 6% of infants experiencing mild liver enzyme elevations, which were transient and did not result in long-term complications.

Paracetamol has been evaluated as a promising alternative to conventional cyclooxygenase inhibitors such as ibuprofen and indomethacin for treating hsPDA in preterm infants. A study by Tanti et al. demonstrated a high efficacy rate, with 100% of

the infants achieving closure of hsPDA without any reported adverse events, establishing it as both safe and effective [6]. Comparatively, Dani et al. reported that while paracetamol was less effective than ibuprofen in achieving ductal closure after the first treatment course (52% vs. 78%), its comparable constriction effect and favorable safety profile support its use as a first-choice drug, especially in cases where conventional drugs pose risks [7]. Meena et al. found paracetamol to be equally effective as indomethacin and ibuprofen for PDA closure, with the added benefit of a superior safety profile. The study reported fewer side effects, including stable renal and liver function, making it particularly advantageous for neonates at higher risk of complications [8]. Similarly, Oshima et al. demonstrated that high-dose intravenous paracetamol achieved significant PDA closure rates (88%) in infants who were either resistant to or contraindicated for indomethacin or ibuprofen, with no significant adverse effects reported [9].

El-Farrash et al. highlighted the efficacy of oral paracetamol, showing results comparable to ibuprofen for first-course treatment and superior outcomes in second-course treatments. Paracetamol was particularly effective in reducing PDA size and improving echocardiographic measures, establishing its role as a reliable first-line therapy [10]. Bouazza et al. emphasized the importance of dosage optimization, noting that while the standard dosing effectively inhibited PDA contraction in most neonates, extremely preterm infants (<27 weeks gestation) required specific dosing adjustments due to reduced efficacy in this subgroup [11].

Conclusion

The study's findings imply that paracetamol is a useful therapy for hemodynamically significant patent ductus arteriosus in premature infants. It provides a non-invasive substitute for various pharmaceutical treatments such as indomethacin or surgical ligation, and it has a 70% PDA closure rate. The long-term advantages of paracetamol in this patient population require more research, despite the fact that a sizable percentage of newborns displayed respiratory improvements. There were very few minor side effects and the medication was well tolerated. Birth weight may influence the clinical response to paracetamol, according to the statistical analysis, however this difference was not statistically significant. It might be possible to better understand the connection between birth weight, gestational age, and future research with bigger sample sizes and a more varied cohort.

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