Journal of
Neonatology and Chronic Pediatric Conditions

Research Article Open Access

Efficacy of Paracetamol in the Closure of Hemodynamically Significant Patent Ductus Arteriosus in Preterm Infants: A Single-Center Study from a Moroccan Neonatal Intensive Care Unit

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Received Date: February 16, 2026 **Accepted Date:** March 03, 2026 **Published Date:** March 06, 2026

Citation: A Ayad, S. Sghir, M Sellouti, M Bahous, R Abilkassem (2026) Efficacy of Paracetamol in the Closure of Hemodynamically Significant Patent Ductus Arteriosus in Preterm Infants: A Single-Center Study from a Moroccan Neonatal Intensive Care Unit. J. Neonatol. Chronic Pediatr. Conditions 2: 1-8

Abstract

Background: Hemodynamically significant patent ductus arteriosus (hsPDA) remains a frequent morbidity in preterm infants. While non-steroidal anti-inflammatory drugs are traditionally used for pharmacologic closure, paracetamol has emerged as a potential alternative with a favorable safety profile.

Objective: To evaluate the efficacy of paracetamol in achieving ductal closure in preterm infants diagnosed with hsPDA in a tertiary neonatal intensive care unit.

Methods: This prospective observational study was conducted in the neonatal intensive care unit of the Military Hospital of Rabat between January 2023 and December 2025. A total of 40 preterm infants diagnosed with hsPDA based on clinical and echocardiographic criteria between days 3 and 14 of life were included. Gestational age ranged from 28 to 35 weeks, and birth weight from 1000 g to 2500 g. All neonates received paracetamol at a dose of 15 mg/kg every 6 hours for 3 days. Echocardiographic reassessment was performed after completion of therapy to evaluate ductal closure.

Results: Effective ductal closure was achieved in 32 patients (80%) after a single treatment cycle. Five infants (12.5%) required a second course of paracetamol to obtain closure. Two patients (5%) had a residual ductus without hemodynamic significance and did not require further intervention. Surgical ligation was necessary in one case (2.5%) due to persistent hemodynamically significant PDA despite medical therapy.

Conclusion: Paracetamol appears to be an effective and well-tolerated therapeutic option for the closure of hsPDA in preterm infants. Larger randomized studies are warranted to confirm its efficacy and safety in comparison with conventional therapies.

Keywords: Patent ductus arteriosus; Preterm infants; Paracetamol; Neonatal intensive care; Pharmacologic closure

Introduction

Patent ductus arteriosus (PDA) is one of the most common cardiovascular complications in preterm infants, with incidence inversely proportional to gestational age and birth weight. When the ductus becomes hemodynamically significant (hsPDA), it may lead to pulmonary overcirculation and systemic hypoperfusion, contributing to morbidities such as bronchopulmonary dysplasia, necrotizing enterocolitis, intraventricular hemorrhage, and prolonged mechanical ventilation [1].

Pharmacologic closure using cyclooxygenase inhibitors, including indomethacin and ibuprofen, has long been considered first-line therapy. However, these agents are associated with potential adverse effects such as renal impairment, gastrointestinal bleeding, and platelet dysfunction, limiting their use in fragile preterm populations.

Paracetamol has emerged as an alternative therapeutic option for PDA closure. Its mechanism involves inhibition of prostaglandin synthesis at the peroxidase segment of the prostaglandin H2 synthase enzyme, differing from traditional NSAIDs. Increasing evidence suggests comparable efficacy with a more favorable safety profile [2].

This study aims to evaluate the efficacy of paracetamol in achieving closure of hsPDA in preterm infants admitted to the neonatal intensive care unit of the Military Hospital of Rabat.

Methods

All preterm neonates born at <35 weeks of gestation and diagnosed with hemodynamically significant patent ductus arteriosus (hsPDA) were prospectively enrolled in this study after obtaining informed parental consent. The study was conducted in the neonatal intensive care unit of the Military Hospital of Rabat, Morocco, between January 2023 and December 2025. A total of 40 preterm infants meeting inclusion criteria were included.

Neonates with major congenital heart disease, significant structural congenital malformations, life-threatening sepsis with multiorgan failure, intraventricular hemorrhage, renal impairment defined as serum creatinine >1.5 mg/dL, thrombocytopenia <60,000/mm^3, or severe hyperbilirubinemia requiring exchange transfusion were excluded.

For all enrolled neonates, detailed antenatal and perinatal history was obtained, followed by comprehensive general and systemic clinical examination. The diagnosis of hsPDA was established based on combined clinical and echocardiographic criteria.

Clinical suspicion of hemodynamically significant ductus arteriosus was based on features suggestive of cardiac failure and pulmonary overcirculation, including tachypnea, tachycardia, hyperdynamic precordium, bounding peripheral pulses, widened pulse pressure, and persistent or increasing requirement for respiratory support such as continuous positive airway pressure (CPAP) or mechanical ventilation.

Echocardiographic evaluation was performed in all cases by an experienced neonatologist or pediatric cardiologist. hsPDA was defined by the presence of one or more of the following parameters: internal ductal diameter ≥1.5 mm, left atrium-to-aortic root (LA/Ao) ratio >1.6, pulsatile unrestrictive left-to-right ductal shunting, and absent or reversed end-diastolic flow in the descending aorta.

Baseline laboratory investigations, including serum creatinine, total bilirubin, liver function tests, prothrombin time, activated partial thromboplastin time, and stool examination for occult blood, were obtained prior to

initiation of therapy and repeated after 72 hours of treatment to monitor drug safety.

All included neonates received paracetamol either orally or intravenously at a total daily dose of 60 mg/kg/day administered in four divided doses (15 mg/kg every 6 hours) for three consecutive days. Oral paracetamol suspension was administered via orogastric tube in enterally fed neonates, while intravenous paracetamol was used in cases of feeding intolerance or contraindication to enteral administration. Supportive neonatal intensive care management was continued as clinically indicated.

Follow-up echocardiography was systematically performed after completion of the 72-hour treatment course to assess ductal closure, residual shunt, or persistence of hsPDA. Decisions regarding the need for a second treatment cycle or surgical ligation were made based on echocardiographic findings and clinical evolution.

Table 1: Demographic and Clinical Characteristics of the Study Population

Characteristic	n (%) / Range
Total number of babies	40
Gestational age	28–35 weeks
Birth weight	1000–2500 g
Male/Female	23 / 17
Age at enrollment	3–14 days
Resuscitation at birth	26 (65%)
Respiratory distress syndrome (RDS)	23 (57.5%)
Surfactant therapy	20 (50%)
Mechanical ventilation	17 (42.5%)
CPAP support	23 (57.5%)
Congestive cardiac failure (CCF)	26 (65%)
Bounding peripheral pulses	37 (92.5%)

Table 2: Echocardiographic Findings of Hemodynamically Significant PDA

Echocardiographic findings	Number of babies (n=40)	(%)
Diameter of the ductus ≥ 1.5 mm	40	100%
Left atrium-to-aortic root ratio > 1.6	37	92.5%
Reversal of flow in the descending aorta	29	72.5%

Results

A total of 40 preterm neonates diagnosed with hemodynamically significant patent ductus arteriosus (hsPDA) were included in the study. Baseline demographic, clinical, and echocardiographic characteristics are summarized in Tables 1 and 2.

Post-intervention echocardiographic evaluation performed after completion of paracetamol therapy (Table 3) and table 4 after completion of the first 72-hour course of paracetamol, complete ductal closure was achieved in 32 of 40 neonates (80%).Five additional infants with persistent hsPDA received a second treatment cycle, resulting in closure in five cases.Overall, complete closure was achieved in

37 neonates (92.5%).Two infants had a residual non-hemodynamically significant shunt, and one required surgical ligation.

Clinically, significant improvement was observed following treatment. Oxygen requirement decreased progressively, and signs of congestive cardiac failure resolved within 3–4 days after initiation of therapy. Among neonates who required invasive mechanical ventilation, successful extubation was achieved within 3–5 days following treatment.

No significant adverse events were observed during the course of paracetamol therapy. Specifically, there were no cases of gastrointestinal bleeding, renal impairment, hepatic dysfunction, or thrombocytopenia attributable to the intervention.

Laboratory parameters assessed before and after treatment, including renal function tests, liver enzymes, coagulation profile, and bilirubin levels, remained comparable. The differences observed between pre- and post-treatment values were not statistically significant, confirming the favorable safety profile of paracetamol in this cohort.

Table 3: outcome after paracetamol treatment

Outcome	n (%)
Closure after first course	32 (80%)
Closure after second course	5 (12.5%)
Residual shunt	2 (5%)
Surgical ligation	1 (2.5%)
Total complete closure	37 (92.5%)

Table 4: Post-intervention Echocardiographic Findings

Echocardiographic finding	Total number of babies (n = 40)	(%)
Ductal diameter		
Closed	37	92.5%
Residual shunt 1–1.5 mm	2	5%
Persistent hsPDA (>1.5 mm)	1	2.5%
Left atrium-to-aortic root ratio < 1.6	39	97.5%
Reverse flow in the descending aorta	0	0%

Table 5: Laboratory Parameters Before and After Paracetamol Therapy (n = 40)

Parameter	Before Treatment	After Treatment
Serum creatinine (mg/dL)	0.3	0.5
AST (U/L)	15	14
ALT (U/L)	14	7
Total bilirubin (μmol/L)	47	26
Platelet count ($\times 10^3/mm^3$)	180	145

Discussion

In the present study, we evaluated the efficacy and safety of paracetamol for the pharmacological closure of hemodynamically significant patent ductus arteriosus (hsPDA) in preterm infants born at <35 weeks of gestation. Our findings demonstrate a high rate of ductal closure, with complete echocardiographic closure achieved in 92.5% of neonates and only one patient requiring surgical ligation. In addition, clinical improvement was rapid, with resolution of congestive cardiac failure and reduction in respiratory support requirements within a few days of therapy initiation. No significant adverse events were observed, and laboratory safety parameters remained stable [3].

These results are consistent with growing evidence supporting paracetamol as an effective alternative to cyclooxygenase inhibitors for PDA closure. Since the first report by Hammerman et al. in 2011 describing successful ductal closure using paracetamol, multiple observational studies and randomized trials have confirmed its efficacy. Reported closure rates in the literature range between 70% and 90%, depending on gestational age, ductal size, and timing of therapy initiation [4].

The high closure rate observed in our cohort is biologically plausible given the known mechanism of action of paracetamol on the peroxidase segment of prostaglandin H2 synthase. Under the relatively low peroxide conditions present in the ductal tissue, this mechanism may effectively reduce prostaglandin synthesis and promote ductal constriction.

El-Mashad et al. conducted a randomized controlled trial comparing paracetamol and ibuprofen and demonstrated comparable closure rates between the two drugs, with fewer renal and gastrointestinal side effects in the paracetamol group. Similarly, Dang et al. reported noninferiority of paracetamol versus ibuprofen in preterm neonates, reinforcing its therapeutic potential [5,6].

A recent meta-analysis by Ohlsson and Shah including randomized and quasi-randomized trials concluded that paracetamol is as effective as ibuprofen for ductal closure, particularly when administered enterally [7]. Moreover, paracetamol showed a more favorable safety profile, especially regarding renal perfusion, platelet function, and risk of necrotizing enterocolitis.

The mechanism by which paracetamol induces ductal constriction differs from that of non-steroidal anti-inflammatory drugs. Rather than inhibiting cyclooxygenase directly, paracetamol acts at the peroxidase segment of prostaglandin H2 synthase, reducing prostaglandin production under low peroxide conditions such as those present in the ductus arteriosus. This distinct pathway may explain its efficacy even in cases where ibuprofen fails.

In our cohort, clinical improvement paralleled echocardiographic closure. Oxygen requirements decreased rapidly, and ventilated neonates were extubated within 3–5 days, suggesting meaningful hemodynamic benefit beyond anatomical closure. Similar respiratory outcomes have been described in prior neonatal studies, where successful PDA closure translated into shorter ventilation duration and improved pulmonary mechanics [8].

Importantly, no significant hepatic, renal, hematologic, or gastrointestinal adverse effects were observed in our study. This finding aligns with safety data from Terrin et al. and Roofthooft et al., who reported minimal toxicity even with repeated courses. The absence of significant laboratory derangement in our cohort further supports the short-term safety of paracetamol in fragile preterm populations [9].

The absence of a control group receiving ibuprofen or indomethacin represents a significant limitation of this study. Therefore, our findings should be interpreted as observational evidence of efficacy rather than definitive proof of superiority. Randomized comparative trials remain necessary to establish paracetamol as first-line therapy.

From a practical standpoint, paracetamol offers several advantages, particularly in resource-limited settings. It is widely available, inexpensive, and easier to administer than indomethacin, which requires strict renal and platelet monitoring. In centers where access to ibuprofen or surgical ligation is limited, paracetamol represents a valuable therapeutic option.

Nevertheless, some considerations remain. Clo-

sure rates may be lower in extremely low birth weight infants or when treatment is initiated late. Furthermore, long-term neurodevelopmental and pulmonary outcomes following paracetamol exposure require further investigation, as current data remain limited [10].

Our study has certain limitations. It is a single-center study with a relatively modest sample size and lacks a comparative control group receiving ibuprofen or indomethacin. However, it reflects real-world clinical practice and provides valuable data from a North African tertiary neonatal unit, a region underrepresented in PDA pharmacotherapy literature.

Conclusion

Paracetamol appears to be an effective and well-tolerated therapeutic option for the management of hsPDA in preterm infants. However, given the absence of a comparative control group, these findings should be interpreted with caution. Larger randomized controlled trials are required before recommending paracetamol as a universal first-line treatment.

Conflict of Interest

The authors declare that they have no conflicts of interest related to this study.

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