RESEARCH ARTICLE

PDA Therapy in Preterm Infants: Early Treatment (NSAID, acetaminophen or combination) versus Watchful Waiting

Alaa Mahmoud Roushdy[1], Tarek M. AbdelRahman[2], Mahmoud Abozaid Mohamad[2*], Hazem M. A. Farrag[2]

[1]*Cardiology Department, Congenital and structural heart diseases unit, Ain Shams University hospitals, Cairo, Egypt.*
[2]*Cardiology Department, Faculty of Medicine, Minia University, Minia, Egypt.*

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ABSTRACT

Drug therapy targeted for PDA closure is one of the most controversial topics, especially among preterm infants. NSAIDs have been the most widely prescribed drugs for this purpose. The argument included early drug treatment versus watchful waiting (i.e., non-pharmacological strategy) and single versus combination therapy. Previous studies concluded that early use of NSAIDs like ibuprofen resulted in a high rate of nonsurgical closure of PDAs in most treated preterm infants. Recently, the impact of early use of ibuprofen among preterm infants was studied in 2 trials. One concluded that early ibuprofen administration wasn't related to a lower risk of death or severe bronchopulmonary dysplasia than a placebo. The other one concluded that early PDA therapy was associated with lower rates of deaths, and this effect was pronounced among groups who required invasive ventilation. Considering that acetaminophen has fewer adverse effects, a novel strategy using combination therapy (NSAID + acetaminophen) had emerged - for pharmacological PDA closure in preterm infants - as an alternative to NSAID alone with similar efficacy and fewer side effects

Keywords: NSAIDs, PDA, Ibuprofen, preterm infants.

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INTRODUCTION

PDA represents 5–10% of all CHD

PDA incidence is inversely correlated with birth weight and GA, with preterm newborns having the greatest recorded rate (GA less than 30 weeks). PDA among extremely preterm infants represents a major CV issue with increased mortality and morbidity.[1] Non-steroidal anti-inflammatory drugs (mainly indomethacin and ibuprofen) are the main drugs used for pharmacological PDA closure through inhibition of cyclooxygenase enzyme that leads to peripheral vasoconstriction Since a large portion of PDAs show spontaneous closure due to many side effects of the NSAIDs, there is a big controversy regarding the safety, efficacy, and regimens of these drugs and possible alternatives.[2] Combination therapy (acetaminophen + NSAIDs) is a novel approach that could be an alternative to the NSAIDs alone approach, being more effective and having fewer side effects.[3]

Mechanism of action of NSAIDs and paracetamol in PDA closure

As shown in this figure, different targets for NSAIDs and paracetamol lead to diminished production of prostaglandins ►, ductal smooth muscle contraction ►, vasa vasorum hypoxia, and lastly, ductal closure [4]

Comparing the safety and efficacy of NSAIDs and Paracetamol

NSAIDs vs. Paracetamol

As regards efficacy, many studies found similar efficacy between NSAIDs and Paracetamol, as shown in this table. [5]

As regards safety, when compared with indomethacin, paracetamol was related to lower rates of creatinine rise, GIT bleeding, and NEC without significant difference in other parameters (mortality, BPD, or ROP requiring intervention1). When compared with ibuprofen, paracetamol was related to a lower risk of hyperbilirubinemia and renal impairment.[6]

**Author for Correspondence: ziamahmoud4@gmail.com*

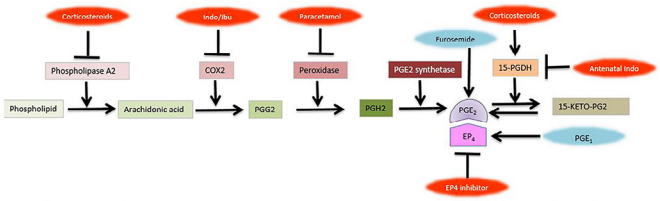

Figure 1: Mechanism of action of NSAIDs and Paracetamol

Table 1: PDA closure rates

	PDA closure rates		
	paracetamol	*ibuprofen*	*Indomethacin*
Dani 20204	42/52 (81%)	44/49 (90%)	n/a
Shahmirzadi 202122	22/23	16/17	n/a
Meena 202014	15/35	13/35	8/35
El-Mashad 20165	80/100	77/100	81/100

Which NSAID (ibuprofen Vs. indomethacin)

As regards efficacy, the 2020 Cochrane Review concluded no significant difference between ibuprofen & indomethacin as regards PDA closure rates. In extremely preterm infants, indomethacin was associated with higher PDA closure rates, but this wasn't statistically significant [7]

Many RCTs suggested an improved safety profile with ibuprofen (lower serum creatinine in the ibuprofen group than in the indomethacin group) (Shah SS 2020). There was no statistical difference between the two drugs in terms of NEC and IVH10 and .[8]

Which dose and which regimen

High-dose ibuprofen was linked to noticeably greater PDA closure rates than standard regimens. High dose ibuprofen regimen starts with more than 10 mg/kg, an average of 15mg/kg, followed by two doses of 7.5 – 10mg/kg, with 12-24 hours intervals between each dose (total dosing is 3 doses). High rates of NEC, IVH, or oliguria24 didn't accompany the high-dose regimen. To improve PDA closure rates with ibuprofen, an escalation regimen was studied versus a standard regimen. Escalation regimen for postnatal age had been given for 3 successive days: 10/5/5mg/kg/dose, 14/7/7mg/kg/dose, 18/9/9mg/kg/dose, before the 70th h of life, 70th-108th h of life, after 108th h of life respectively). Increasing the dose regimen wasn't as efficient as the earlier treatment.[9]

Oral Vs. parenteral route

Oral ibuprofen was more effective than the IV route. Following IV administration, there was a higher peak concentration that could cause transient renal dysfunction and, consequently, volume overload that might restrain PDA closure.[10]

Combined Vs. Monotherapy treatment

Due to the different mechanisms of action of ibuprofen and r, as shown in Figure 1, combining both drugs might lead to a synergistic effect and improved efficacy regarding PDA closure rates.[11]

Evidence from RCTs

There are two small RCTs. One compared ibuprofen + paracetamol Vs ibuprofen monotherapy. PDA closure rates were higher in the combination arm than in monotherapy.[12] Another one studied ibuprofen Vs paracetamol vs ibuprofen + paracetamol. PDA closure rates and safety profiles were similar between the 3 groups. The inclusion of mature preterm infants (one of the limitations of this study), where there is a high chance of spontaneous closure, may explain the study results. Recently, A Systematic Review concluded that combination therapy is more effective than monotherapy.[13]

Medical vs. conservative management

Recently, Gupta et al. concluded that rates of deaths and significant BPD weren't reduced by early ibuprofen administration in extremely preterm infants with large PDAs. BPD incidence is increased mainly in infants with large PDAs requiring MV for more than one week. This was confirmed in a large cohort study done by Qian A et al., who concluded that the risk of death was reduced in extremely preterm infants with PDAs who received PDA therapy. This valuable result was pronounced in infants who needed MV.[14]

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