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Review Article

Paediatrics Section

Different Medicinal Treatment Modalities in the Management of Patent Ductus Arteriosus in Paediatric Population- A Narrative Review of Available Drug Approaches

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BY-NC-ND

ABSTRACT

Regardless of the size of a patient's Patent Ductus Arteriosus (PDA), it is crucial for paediatric and adult cardiologists to have a thorough understanding of the condition's origin, clinical ramifications, and treatment options. Possessing a PDA, no matter how little, might cause complications. Ibuprofen and indomethacin, both cyclo-oxygenase (COX) inhibitors, are used as the gold standard pharmacologic therapy for closing a PDA that has been produced surgically. These non selective COX inhibitors bring about ductal constriction, in addition to lowering the synthesis of prostaglandin. However, these drugs may also have a broad array of unintended consequences. Interest in paracetamol for PDA constriction has recently increased due to fewer adverse effects than indomethacin or ibuprofen. Evidence that paracetamol is now a topic of intense study lends credence to this hypothesis. Information on the long term effects of paracetamol is scarce in paediatric population.

Keywords: Acetaminophen, Ibuprofen, Indomethacin, Paracetamol

INTRODUCTION

The ductus arteriosus is a necessary part of foetal circulation that diverts cardiac output towards the placenta and away from the lungs to support systemic oxygenation [1]. It is a vascular component that connects the two main arteries from the heart and joins the proximal descending aorta to the pulmonary artery, proximate to the beginning of the left branch pulmonary artery. Using this shunt, oxygenated blood from the placenta is able to enter the systemic circulation of the developing newborn. This allows the blood to avoid the foetus's underdeveloped lungs. The ductus arteriosus must close as quickly as possible after birth, in order to enable the circulatory system to make the transition to the mature, split pattern of arteriovenous circulation. This shift must occur before the baby can breathe on its own [2]. The circulation of placenta is clamped and eliminated at birth, which reduces the resistance in the pulmonary vascular bed, and thus, the lungs adapt for gas exchange and as a source of oxygenation; therefore, the Ductus Arteriosus (DA) is no longer required. In normal-term infants, the DA closes in >90% by 48 hours and completely by 96 hours of age [1].

The most prevalent cause of PDA, also known as a failure of ductus arteriosus closure, is premature delivery. Premature birth is the most predictable cause. As early as seven days of age, up to 64% of newborns who are 27 to 28-week-old and 87% of infants who are 24-week-old have an open ductus [2]. It is the greatest reason of morbidity in preterm neonates, particularly in babies who weighed less than 1,000 gm at birth or who were delivered at a gestational age of less than 28 weeks [3]. Gestational age and weight are inversely related to PDA in preterm neonates. Specifically, PDA is present in 80% of infants weighing less than 1,200 gm at birth, compared to 40% of infants weighing less than 2,000 gm at birth [4-6]. Furthermore, symptomatic PDA is present in 48% of infants with a birth weight of less than 1,000 gm [7]. This is an extremely high number in comparison to the incidence rate, which is 2/1000 among neonates who have reached their full gestation [3]. After the first few weeks of a person's existence, it is quite rare for ductal patency to persist. The magnitude of the PDA and the patient's pre-existing circulatory condition are the two primary factors that define the PDA's influence on the patient's physiology as well as the therapeutic significance of the PDA. Sometimes, the PDA is "silent," which means that it is not immediately visible clinically but is detected by echocardiography that was meant for another cause. It's possible that the personal digital assistant will be on the smaller side, on par with the industry norm, or on the larger side [8]. The feasibility and safety of performing a percutaneous PDA closure in babies was investigated in a study that was conducted by Backes CH et al., it was shown that the technical success rate of percutaneous PDA closure was 92.2% [9]. The incidence of all adverse events was 23.3%, and the incidence of clinically severe adverse events was 10.1% [9]. PDA's roots, clinical symptoms, and treatment choices are all things that cardiologists who work with children and adults need to be familiar with. No matter how large the PDA is, there is always the possibility of problems [3]. Furthermore, it seems that the timing of the PDA treatment that is being advised is also quite important [10]. In another study, the incidence of bronchopulmonary dysplasia was significantly lower in early group survivors than in late group survivors [11]. Furthermore, these beneficial effects of early surfactant treatment were still present after controlling for the various confounding factors that were used in the logistic models.

Hence, the present review discusses various drug therapies available and their technical success, efficacy, and safety demonstrated by various studies in the treatment of PDA. As a result, the findings of present research contribute to overall comprehension of the numerous PDA treatment drug choices.

Medicinal Approach

There are a variety of treatment options available, such as those that are conservative (that is, medical) or those that are medical, pharmacologic, or surgical. The conservative and medical treatment consists of a few different components, including a moderate restriction of fluid intake, increased airway pressures, and supportive care. Medication such as indomethacin,

ibuprofen, or acetaminophen are a few examples of the kinds of drugs that might be used during pharmacologic treatment [12]. Therefore, the usage of non selective COX inhibitors serves as the pharmacological beginning for the therapy of medical conditions. These inhibitors bring about ductal constriction, in addition to lowering the synthesis of prostaglandin. Both indomethacin and ibuprofen are non selective COX inhibitors, although ibuprofen and indomethacin have garnered the most attention from researchers, while indomethacin has seen the most clinical application [3]. Treatment may either be preventive, presymptomatic, or symptomatic, and it can fall into any of these three categories. Long term morbidities such as chronic lung disease, retinopathy of prematurity, and neurodevelopmental delay are all associated with prematurity related developmental halt [12]. It is recommended that patients who are at high risk for PDA, or who were born weighing less than 1,000 gm attempt non pharmacologic ways of therapy first, before turning to pharmaceuticals as a therapeutic option. When pulmonary vascular resistance is still significant in the days following delivery, therapy is often not recommended, even though it is possible that treatment is not always required. However, therapy alternatives should be researched if conservative efforts to manage pulmonary oedema have not been successful by the end of the second week, or if there is evidence of failure in either the heart or the kidneys. After the third week, it is anticipated that the efficacy of pharmacological treatments would begin to wane [10]. In the future, pharmacological treatments for PDA may involve the use of drugs that restrict nitric oxide production and drugs that block prostaglandin receptors.

Indomethacin

Indomethacin is an effective inhibitor of the production of prostaglandin E2, and as a result, it reduces inflammation. The considerable rise in oxygen pressure that occurs in the blood shortly after delivery is the primary component that is responsible for the closure of the ductus arteriosus. This change occurs during the first few minutes after birth. This transformation happens not long after the baby is born. The hormone prostaglandin E2, which has the opposite effect of oxygen and so tends to prevent the ductus arteriosus from closing, is responsible for relaxing smooth muscle. This effect is generated by the hormone's ability to relax smooth muscle. There is a possibility that the presence of oxygen is responsible for this phenomenon. It is possible that the fact that oxygen causes smooth muscle to contract might give some insight into why this is happening [13]. The first dosage for the short course therapy is 0.2 mg/kg, and the subsequent doses are as follows: 0.1 mg/kg for neonates less than two-day-old, 0.2 mg/kg for newborns aged 2-7 days, and 0.25 mg/kg for babies more than seven-day-old. The total dose for the short course treatment is 0.5 mg/kg. It is essential to provide a single dose of 0.1 mg/kg once per day for a period of six days in order to treat the condition on a long term basis. This is the smallest possible dosage of medicine that should be taken. Both procedures are examples that are included in the Standard Operating Procedure (SOP) [12]. The seal of the ductus arteriosus is broken in preterm newborns who have respiratory distress syndrome and have high levels of prostaglandin E2. These preterm infants also have high amounts of prostaglandin E2. The elevated levels of prostaglandin E2 are to blame for this phenomenon (PDA). It is possible that preterm infants might benefit from receiving prophylactic indomethacin by a continuous infusion of moderate dosages of indomethacin. This is something that is worth investigating. Because of the likelihood that premature babies might gain from this, this potential now exists. When compared to babies that were carried to full term, preterm neonates had a lower likelihood of experiencing a positive outcome after the administration of indomethacin [13]. Because of this impact, taking indomethacin may result in a short term decrease in the production of prostaglandins; nevertheless, one need not worry about this happening permanently. Because levels of prostaglandin return to normal within 6-7 days after short term medication is stopped, there is a greater chance that the duct may reopen during long term treatment. This fact contributes to the increased likelihood that the duct will reopen. The possibility of the duct reopening as a result of this is increased. This is only one of the many reasons why it is essential to continue therapy even after it has been completed. If, at the end of the first round of treatment, the PDA is still evident, a second dosage of indomethacin will be administered before the surgical ligation operation is carried out. This is because indomethacin has a high proportion of effectiveness in preventing PDA [14]. There is some evidence that taking indomethacin as a prophylactic approach may lower the risk of having PDA, but there is no evidence that this reduces the risk of developing BPD. It's possible that this is because of the detrimental effects that it has as a side effect on oxygenation and the production of oedema, but it's more likely that this is just a coincidence [15]. Liebowitz M and Cluyman RI reported that indomethacin reduces BPD or death in comparison to delayed conservative PDA management [16].

Ibuprofen

The mechanism of action of Ibuprofen is, it acts by inhibiting synthesis of prostaglandin [17]. Mitra S et al., conducted a meta-analysis and reported that a high dose of oral ibuprofen (15-20 mg/kg followed by 7.5-10.0 mg/kg every 12-24 hours for a total of three doses) was found to be associated with a significantly higher likelihood of PDA closure than two of the most widely used forms of pharmacotherapy {i.e., standard doses of intravenous (i.v.) ibuprofen and intravenous indomethacin} [18]. The ibuprofen dose that is traditionally used (10 mg/kg, 5 mg/kg, and 5 mg/kg, each given at 24 hour intervals) is based on old pharmacokinetic data obtained from the experiences of preterm infants [18]. In another meta-analysis by Ohlsson A et al., ibuprofen was found to be as effective as indomethacin to close a PDA and causes fewer transient adverse effects on the kidneys and reduces the risk of Necrotising Enterocolitis (NEC), a serious condition that affects the gut [19]. Ohlsson A et al., revealed that a long-term follow-up studies to 18 months of age and to the age of school entry are needed to decide whether ibuprofen or indomethacin is the drug of choice for closing a PDA [19]. The regimen that works for the management of PDA with ibuprofen consisted of three doses. The proposed first dose is 10 mg/kg intravenously which is followed by twice dosages, at 24 and 48 hours later of 5 mg/kg. The subsequent dose(s) should be held if urine output is <0.6 mL/kg/hr till the kidney function has reverted to normal. In case there is a failure in the closure of ductus arteriosus or it reopens laterally, another follow-up course of ibuprofen may be required [17]. Lago P et al., conducted a comparative analysis and reported that ibuprofen has lesser adverse effects in terms of fluid retention and urine output besides much the similar efficacy and safety index in preterm infants who had respiratory distress syndrome in closing PDA in comparison with indomethacin [20]. However, there was no reported incidence of increase in cases of intracranial haemorrhage was observed after treatment with ibuprofen. Ohlsson A et al., reported that Ibuprofen is as effective as indomethacin in closing a PDA and reduces the risk of developing NEC and transient renal insufficiency. Ibuprofen was not associated with any other side effects [21].

Ibuprofen must be used within half an hour of preparation. The dose could be infused over 15 minutes continuously nevertheless it must not be administered in the same i.v. line with total parenteral nutrition. Furthermore, the unused or leftover solution of ibuprofen must be discarded as there is no preservative content in it. About 17.1 mg/mL (equivalent to 10 mg/mL ibuprofen) is the available

concentration of ibuprofen lysine and these vials must be stored away from sunlight at room temperature (20°-25°C) [17].

Paracetamol

More lately, oral or i.v. administration of paracetamol (acetaminophen) gained attention in PDA treatment [22]. However, ductal closure with paracetamol was first reported by Hammerman C et al., who described five cases of haemodynamically significant PDA among preterm infants of gestational age of 26-32 weeks and postnatal age of <35 days, who had either contraindications to ibuprofen therapy or had failed therapy [23]. Ductal closure was achieved in <48 hours after each of these infant patients were treated with off-label oral paracetamol (15 mg/kg per dose six hourly) [23]. Moderate certainty evidence proposes that there is possibly little or no difference in the efficiency between ibuprofen and paracetamol; low-certainty evidence reveals that there is probably no or little difference in efficiency between indomethacin and paracetamol; for low certainty evidence, firstly prophylactic paracetamol might be more effective than placebo/no intervention; secondly, early paracetamol treatment may be more effective than placebo/no intervention; thirdly, probably little or no difference in effectiveness between the combination of paracetamol and ibuprofen versus alone ibuprofen and further there is probably little or no difference between late paracetamol treatment and placebo after the first course of treatment for the closure of PDA [24].

Before paracetamol introduction, in case of contraindication for Non-steroidal Anti-inflammatory Drugs (NSAIDs), such as active or recent intracerebral haemorrhage (<48 h), thrombocytopenia (<50,000/mm^3), bleeding diathesis (meaning INR >1.5 and/or haematuria, blood in the stool, tracheal secretions or at the injection site), sepsis, NEC, intestinal perforation, pulmonary haemorrhage, hepatic damage with severe hyperbilirubinemia, renal dysfunction (oliguria<1 mL/kg/h also after adequate hydration, serum creatinine >110-140 mmol, and Blood Urea Nitrogen (BUN) >14 mmol/L), and hypersensitivity to ibuprofen, the only available solution was surgical ligation with all the connected risks [22]. Mohanty PK et al., studied the role of paracetamol orally in closing Haemodynamically significant PDA (hsPDA) in preterm infants with gestational age <32 weeks in cases where there was a contraindication for ibuprofen and 72.5% infants showed successful response with no major complications reported [25]. Similarly, Surak A et al., also reported that acetaminophen could be used in for the closure of hsPDA [26]. In another meta-analysis by Terrin G et al., the efficacy and safety of paracetamol seemed to be comparable with those of ibuprofen [27].

Recently, concern has been raised about paracetamol's presumed superior safety profile based on reports of neurocognitive impairment after prenatal exposure and of hypotension following i.v. administration. This concern underscores the need for appropriate pharmacodynamic and follow-up studies examining both the route and the dose of paracetamol as well as the population being studied before it can be concluded which is the most effective and safest drug to use when PDA treatment is needed [19]. Valerio E et al., studied the efficacy and safety of i.v. paracetamol for PDA closure in a 23-32 week preterm population, as "first-line" (when traditional ibuprofen treatment was contraindicated) or "rescue" treatment (after ibuprofen failed) and reported that the cumulative efficacy of consecutive cycles of i.v. paracetamol on PDA closure was confirmed after both "first-line" and "rescue" treatment, the overall PDA closure rates being, respectively, 56.7% and 61.1% (p=0.762) after two cycles and 63.3% and 77.8% (p=0.295) after three cycles [28]. No toxicity was apparent after either "first-line" or "rescue" i.v. paracetamol treatment. Yang B et al., reported that the arterial duct closure rate was comparable between the acetaminophen (70.5%) and ibuprofen groups (76.7%), plasma and urinary Prostaglandin E2 (PGE2) levels in the acetaminophen group were significantly decreased than those in the ibuprofen group and the incidence of oliguria was less in acetaminophen group (2.3%) than the ibuprofen group (14.0%); however, this difference was not significant statistically [29]. Balachander B et al., also reported that paracetamol is as effective as ibuprofen for PDA closure in preterm neonates but ibuprofen possessed an enlarged risk for acute renal injury in comparison to paracetamol [30]. Xiao Y et al., concluded that paracetamol can induce early PDA closure without significant side effects but its efficacy is not superior to that of indomethacin [31]. Sinha R et al., the PDA closure was achieved within 48 hours of treatment with oral paracetamol in a dose of 15 mg/kg eight hourly, with no reported complication in preterm neonates who had failed or had absolute contraindication with ibuprofen [32]. More studies pertaining to the efficacy of paracetamol in the treatment of PDA is demonstrated in [Table/Fig-1] [28-35].

Author	Year	Type of study	Sample size	Drug used	Conclusion/Inference
Balachander B et al., [30]	2020	Retrospective study	110	Paracetamol and ibuprofen	The infants who received ibuprofen had a greater occurrence of acute renal injury (RR 0.33, 95% CI 0.13-0.85, p=0.024).
Xiao Y et al., [31]	2020	Meta-analysis	15 trials (N=1,313)	Paracetamol, ibuprofen, indomethacin.	No significant difference existed between paracetamol and indomethacin as well as paracetamol and ibuprofen except for the less mean number of days required for closure of PDA, decreased risk of gastrointestinal bleeding and hyperbilirubinemia in paracetamol group.
Guimarães AFM et al., [33]	2017	Retrospective study	87	Acetaminophen	The overall PDA closure rate after either one or two cycles was 74.7% (65/87).
Valerio E et al., [28]	2016	Randomised control trials	-	Paracetamol	The cumulative efficacy 56.7% and 61.1% (*p*=0.762) after two cycles and 63.3% and 77.8% (*p*=0.295) after three cycles. No toxicity was apparent after either "first-line" or "rescue" i.v. paracetamol treatment.
Yang B et al., [29]	2016	Randomised control trials	87	Ibuprofen and acetaminophen	The incidence of oliguria was less in acetaminophen group (2.3%) than in ibuprofen group (14.0%) observed among the sPDA infants
Härkin P et al., [34]	2016	Controlled, double-blind study	63	Paracetamol and placebo	Ductus closed rapidly in the paracetamol group (hazard ratio 0.49, 95% CI 0.25-0.97, p=.016).
Aikio O et al., [35]	2014	Retrospective study	105	Paracetamol and placebo	The incidence of PDA decreased from 30.7% to 14.7%
Sinha R et al., [32]	2013	Prospective Case study	10	Paracetamol	The PDA closure was attained in <48 hours with no reported complications.

[Table/Fig-1]: Literature revealing the efficacy of paracetamol in the treatment of PDA [28-35].

CONCLUSION(S)

The administration of a COX inhibitor i.e., indomethacin or ibuprofen is considered as the gold standard for PDA closure, but there is a possibility of severe adverse effects with these drugs. Furthermore, due to less adverse effects of paracetamol compared to indomethacin or ibuprofen, the present review derives consequence that the paracetamol is clinically efficient for the treatment of PDA closure in a Very Low Birth Weight (VLBW)/Extremely Low Birth Weight (ELBW) preterm population. However, Randomised Control Trials (RCTs) are further warranted to broaden investigations reporting the efficacy and safety of paracetamol for PDA closure in preterm neonates.

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