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Efficacy of Indomethacin for Closure of Patent Ductus Arteriosus



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ABSTRACT

Background: While in the womb, the circulation of the fetus differs from the circulation the neonate will have when born. Before the infant is born, there is a shortcut that the blood travels through called the ductus arteriosus (DA). **Purpose:** The purpose of this study was to determine if indomethacin is more effective than other treatment options in closing patent ductus arteriosus (PDA). **Method:** This was a thorough review of pertinent literature. The patient, intervention, comparison, and outcome (PICO) question used for this study was: In newborns with a PDA, what is the efficacy of using indomethacin for closure of the PDA compared to other treatment modalities? **Findings:** Indomethacin tends to have higher efficacy with the age-adjusted doses. Paracetamol should be used cautiously as it is still understudied with a prevalence of bias and lack of representation. Indomethacin, paracetamol, and ibuprofen are equally effective in treating PDAs. **Conclusion:** Based on the findings, it can be assumed that not one medication treatment is more effective than the other.



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1. INTRODUCTION

PDA is a common heart condition among newborns, which causes the mixing of oxygenated and deoxygenated blood, leading to inadequate perfusion [1]. There are three main treatments for treating a PDA: indomethacin, paracetamol, and ibuprofen. The purpose of this study was to determine if indomethacin is more effective than other treatment options in closing PDAs.

In the womb, the circulation of the fetus differs from the circulation the neonate will have after birth. Before the infant is born, there is a shortcut that the blood travels through called the DA. The DA allows for the blood to bypass the lungs by serving as a shunt between the pulmonary artery and the aorta [2]. In the womb, blood cannot be oxygenated by the fetus's lungs due to the lungs being filled with amniotic fluid, instead, the placenta oxygenates the blood of the fetus [1]. This bypass prevents the fetus from developing life-threatening cardiac problems while in the womb [3]. However, after the infant is born these adaptations in the infant's circulation are no longer needed. If the DA remains patent after birth, it is then termed a PDA. A DA that is open for more than 24 hours after birth can cause inadequate perfusion and lead to life-threatening cardiac changes. Hemodynamically significant PDA has many complications for preterm and low birth weight neonates and is better to be closed [4]. The PICO question used for this study was: In newborns with a PDA, what is the efficacy of using indomethacin for closure of the PDA compared to using other treatment modalities?

2. METHOD

This review was performed by searching databases for studies that contain information about treatments for PDAs. The database used was the Cumulative Index to Nursing and Allied Health Literature (CINAHL), Google Scholar, and Cochrane database. A general search of treatments for patent ductus arteriosus yielded 987 results. A narrower search was conducted using the keywords ductus arteriosus, patent, drug therapy, nursing, and meta-analysis, therapeutic use, this gave 428 results. A total of 62 results were yielded after narrowing down studies published between 2020 to 2023. The chosen studies were peer-reviewed and mostly from a higher level of evidence. The studies were organized based on the nursing level of evidence [5]. For the level of evidence, 1 is the highest, and 7 is the lowest hierarchy of evidence. Higher levels of evidence

included randomized control trials (RCT), systematic reviews, meta-analysis of RCTs, and studies from the Cochrane database.

3. LITERATURE REVIEW

After reviewing the literature, three pharmacological treatment modalities were found to be effective at treating PDAs. These medications were indomethacin, paracetamol, and ibuprofen (see Figure 1). Each of the medications was found to be effective with no significant difference between them, however, each treatment option has side effects. A summary of the literature review is presented below.

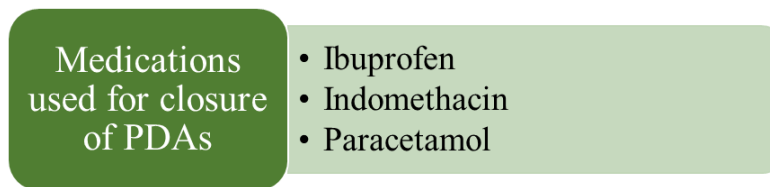


Figure No. 1: Medications commonly used for the closure of PDAs.

Indomethacin Efficacy

Indomethacin is a commonly used non-steroidal anti-inflammatory drug (NSAID) used to treat PDAs [1]. It works by inhibiting the synthesis of prostaglandins which in turn decreases the number of prostaglandins in the infant's blood. The decrease in prostaglandins allows the PDA to close [1]. In a randomized prospective study, Meena et al. [6] discovered the rate of closure after the first course of indomethacin to be 22.86% and the cumulative closure rate was 68%. Raknoo et al. [7] claim that indomethacin has an overall rate of PDA closure of approximately 75-95%.

In another study, Davidson et al. [8] claimed that 55% of infants receiving indomethacin had successful closure of the PDA. The analysis of the pre-and post-treatment echocardiograms showed a significant reduction in the diameter of the PDA. The incidence rate of reversed diastolic flow was also reduced [8]. Desai and Taksande [9] alerted that 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 [9]. Evans et al. [10] in a review of 14 clinical trials (880 infants) found that indomethacin is very effective in closing a PDA, reducing the risk of PDA being open at one week by 70% when compared to no treatment or placebo.

Intrauterine infection and multiple births were identified as potential risk factors for a non-response to prophylactic indomethacin for PDA in preterm infants [11]. Dedeoğlu and Şaşmazel [12] asserted that infants exposed to moderate-to-large PDA requiring intubation and resistant to medical therapy for more than 2 weeks should have surgical ligation as soon as possible. In another study of a small population of premature neonates, there was a trend, but no significant difference, towards increasing PDA closure and lower surgical ligation rates in neonates given indomethacin with more frequent dosing and shorter infusion time [13]. A report in the News Rx [14] signified that preterm newborns are at risk for PDA, and NSAIDs are often used to facilitate PDA closure. However, acute kidney injury is common in critically ill neonates and may be caused by non-steroidal anti-inflammatory drugs. Surveillance of kidney function during indomethacin therapy using more sensitive renal biomarkers may better identify infants who develop acute kidney injury in the context of NSAID use. No association between acute kidney injury during indomethacin therapy and PDA closure was noted. The paucity of serum creatinine values likely underdiagnosed acute kidney injury [14].

Ibuprofen Efficacy

Ibuprofen is an NSAID that works similarly to indomethacin by inhibiting the synthesis of prostaglandins, allowing the PDA to close. Meena et al. [6] found that the rate of closure after the first course of ibuprofen treatment was 37.14% and the cumulative rate was 77.14%. Klerk et al. [15] concluded that 35.5% of infants with a hemodynamically significant PDA (HsPDA) had successful treatment with ibuprofen. However, the dosage also affects the efficacy rate. When the standard dosing is used, the efficacy rate is 32.4% compared to 46.2% when using a postnatal age-adjusted dose. Mitra et al [16] found that a high dose of oral ibuprofen may offer the highest likelihood of hemodynamically significant PDA closure in preterm infants. Conservative management of hemodynamically significant PDA is not likely to increase morbidity and mortality.

Paracetamol Efficacy

Paracetamol can also be used for closure of PDAs. The medication works by inhibiting the peroxidase stage during the synthesis of prostaglandins [3]. Meena et al. [6] identified a 42.46 % closure rate after the initial treatment of paracetamol and a cumulative closure rate of 71.43%. Davidson et al. [8] claimed that 6% of the paracetamol group had achieved closure of the PDA. Interestingly, there were no statistically significant changes in the paracetamol-treated infants between pre- and post-treatment echocardiograms. In a retrospective cohort study, paracetamol was found to be 72.5% effective in closing PDAs [17]. Bitar et al. [18] noted that the efficacy rate was higher with a six-day course of treatment compared to a three-day course of treatment.

Side Effects

Side effects are common when using medications for treatment (see Figure 2). However, when looking at the efficacy of medications, the severity and occurrence of the side effects need to be weighed. Especially when considering benefit versus risk. Bitar et al. [18] acknowledged that while paracetamol and indomethacin are both effective, indomethacin has more side effects.

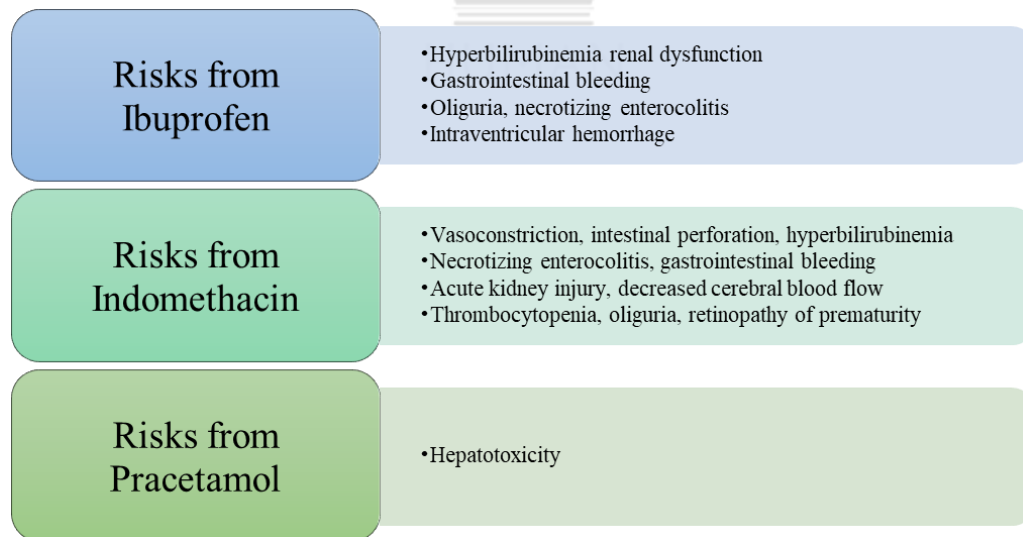


Figure No. 2: Risks Associated with Medications Used for PDA Closure

Indomethacin causes vasoconstriction of the blood vessels that supply the abdominal organs. Due to vasoconstriction, the bowel becomes hypoxic and the risk for perforations increases. When this happens, the infants are at risk of developing necrotizing enterocolitis (NEC).

Indomethacin also increases the risk of the neonate developing an acute kidney injury (AKI); however, indomethacin's long-term effects on renal function are unknown [7,18].

Indomethacin also increases the risk of thrombocytopenia, spontaneous intestinal perforation (SIP), and gastrointestinal bleeding [19]. Indomethacin has been shown to decrease cerebral blood flow causing inadequate cerebral oxygenation. It has been shown that indomethacin use is also correlated with incidences of oliguria, retinopathy of prematurity (ROP), and hyperbilirubinemia [8].

When comparing paracetamol and ibuprofen, both tend to have similar efficacy rates. However, paracetamol tends to have fewer side effects. Even though paracetamol has the least amount of side effects, it should still be used with caution because of the risk of hepatotoxicity [20]. Ibuprofen is associated with a higher risk of hyperbilirubinemia renal dysfunction and gastrointestinal bleeding [17,18]. Other potential side effects of ibuprofen include oliguria, intraventricular hemorrhage, and NEC [15].

Many factors can impact the effectiveness of a medication such as an HsPDA or a non-hemodynamically stable PDA (nHsPDA), the size of the PDA, and the age of the infant at the time of treatment. These factors can impact the decision-making process when deciding whether to give one medication or the other. This means the infant may need further intervention to close the PDA. Davidson et al. [8] included in their findings that 47% of the infants in the paracetamol group needed transcatheter PDA closure (TCPC). It was also pointed out that only 15% of the indomethacin group needed TCPC to treat the PDA.

Summary of Results

Upon reviewing the literature, four themes emerged (see Figure 3). These themes are explained in depth below. The themes presented answer the research question: In newborns with a PDA, what is the efficacy of using indomethacin for closure of a PDA compared to using other treatment modalities? There was an additional theme found that did not answer the research question, but it provided important insight into each treatment modality.

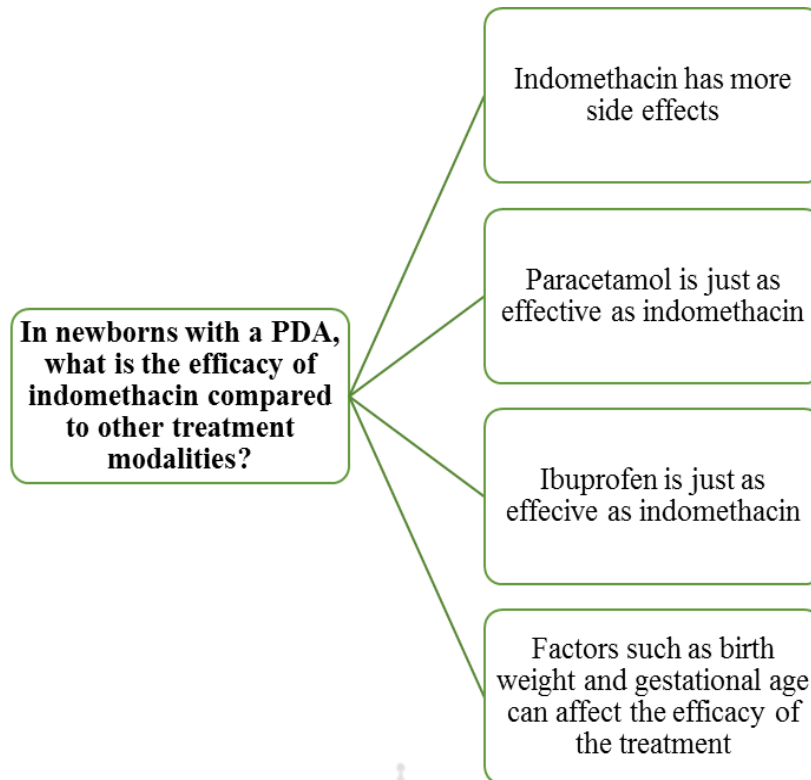


Figure No. 3: Findings for Efficacy of Indomethacin for Closure of PDA

4. DISCUSSION

It was concluded that indomethacin is not the most effective medication to be used. However, paracetamol, ibuprofen, and indomethacin were all equally effective and each had associated side effects. Even providing the patient with a dual medication therapy of paracetamol and ibuprofen together showed no more efficacy than just using one of the medications [3]. However, indomethacin was shown to have more side effects. Davidson et al. [8] concluded that infants with moderate to large PDAs may require further surgical treatment. One strength of this study was that there are multiple treatment options to investigate, and the medications used are effective in treating PDAs. The study is simple to read, and the findings are laid out.

Paracetamol is as Effective as Indomethacin

When comparing paracetamol to indomethacin many of the studies implied that they were not significantly different in their efficacy. The medications work at different stages in the synthesis of prostaglandins [3]. However, this was found to not be clinically significant in determining

their efficacy. Paracetamol was found to have fewer side effects compared to indomethacin [8,18]. It was concluded that they are just as effective in treating PDA. A large study comparing the efficacy and side effects of indomethacin, ibuprofen, and paracetamol found that paracetamol is as effective as indomethacin and ibuprofen in the closure of PDA in preterm neonates and has fewer side effects mainly on renal function, platelet count, and bleeding [4].

Ibuprofen is as Effective as Indomethacin

Ibuprofen and indomethacin are both NSAIDs that similarly inhibit the production of prostaglandins [1,6]. Ibuprofen's efficacy is correlated with the type of dosage used. However, the studies indicated no significant difference between ibuprofen and indomethacin. It was concluded that ibuprofen is just as effective as indomethacin.

Indomethacin has More Side Effects

One major theme that was found throughout this review was that indomethacin has more side effects compared to the other pharmacological treatment options. Indomethacin increases a newborn's risk of NEC due to the vasoconstriction it causes in the abdomen. This vasoconstriction can lead to AKI, however long-term renal effect is unknown. It increases the risk of thrombocytopenia, spontaneous intestinal perforation (SIP), and gastrointestinal bleeding. Indomethacin use can result in reduced cerebral blood flow, oliguria, and ROP [8,19].

Factors Affecting the Type of Treatment

When choosing a course of treatment for a patient, the physician must look at all factors. It was noted that factors such as birth weight, gestational age, current weight, and echocardiographic findings can affect which medication is chosen and how well it works [18, 19]. It was also noted that, in infants with moderate to large PDAs, TCPC was needed to successfully close the PDA [8].

Recommendations

Current recommendations have been made to conduct further studies on each medication. These medications have been effective for the closure of PDAs. However, it is unclear which medication is the most effective. Until there is more concrete evidence to support one medication

as being more effective than another, the current practices should continue as they have. However, a policy review may be required based on these findings. Staff education on the side effects of each medication will be beneficial to ensure the safety of the infants undergoing treatment. It is recommended that when choosing which medication to use to close a PDA the physicians and healthcare team look at the infant as a whole and weigh the benefits and risks carefully (see Figure 4).

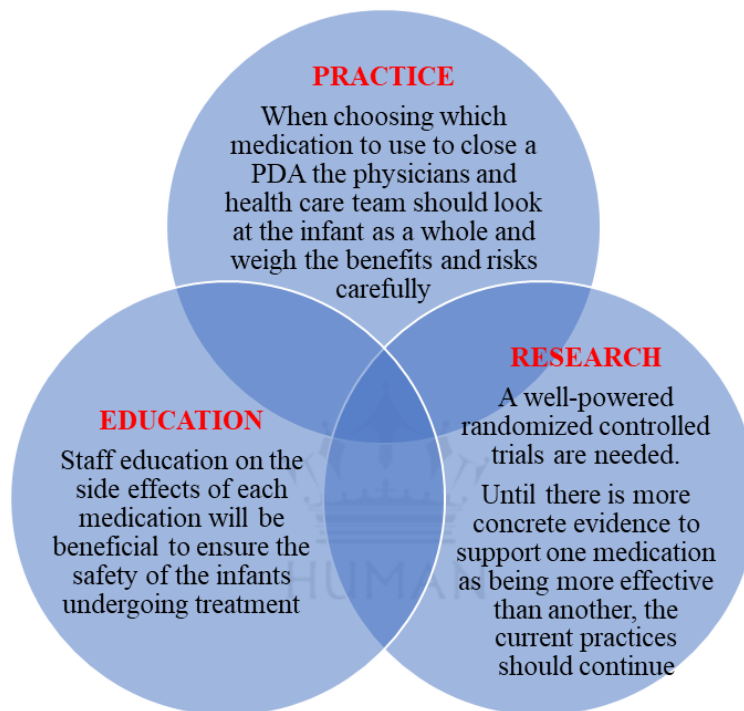


Figure No. 4: Application of Evidence-Based practice for PDA Closure

CONCLUSION

A PDA can cause serious perfusion and cardiac complications in newborns. There are many pharmacological treatment options available to close the PDA. When looking for an answer to the research question in newborns with a PDA, what is the efficacy of indomethacin for closure of the PDA compared to other treatment modalities, three treatment options were evaluated including indomethacin, ibuprofen, and paracetamol. It can be confirmed that risks exist; however, each of the three medications is effective at closing PDAs and the efficacy rate of one medication is not significantly different from the other medications.

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