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Ibuprofen VS. Indomethacin in the Closure of the Patent Ductus Arteriosus (PDA)

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Scholarly Project

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A premature infant is at high risk for many complications and multiple morbidities. A patent ductus arteriosus (PDA) is just one complication that often presents with prematurity and can be a major cardiac defect creating variations of altered cardiac function and systemic circulation. The severity of effects a PDA can produce depends on factors such as gestational age of the infant, weight of the infant, size of the defect, and the overall health of the neonate.

This topic is significant in the medical field because infants born prematurely are seen to have a high rate of their patent ductus arteriosus (PDA) not closing after birth resulting in complications. When the PDA does not close, it produces left to right shunting of the blood in the heart. Left to right shunting is associated with pulmonary congestion and decreased blood flow to vital organs (Linder et al., 2010). Prior to the introduction of ibuprofen, the only alternative to indomethacin was a surgical ligation. This includes a thoracotomy with potentially serious complications including chylothorax, infections, respiratory compromise, and death, which is why this should be considered the last option (Sekar & Corff, 2008).

Ibuprofen was introduced as an alternative medication to close the PDA, but it is not being utilized in all institutions. The purpose of this project is to explore the use of ibuprofen as the first line of treatment for the closure of the PDA in the neonatal population. Information produced could aid in the development of a new standard of care in the neonatal intensive care units. Explanation of ibuprofen's safety and efficacy as well as why it may be preferable to indomethacin will be supported.

### **Definition and Description of the Problem**

A ductus arteriosus (DA) is a bridge or canal connecting the pulmonary artery to the descending aorta during fetal life (Rowan & Grenville, 2004). This opening is vital during fetal

circulation in order for a significant portion of the blood to bypass the pulmonary circulation and shunt to the body and eventually back to the placenta to be reoxygenated (Sekar & Corff, 2008). The placenta is considered the fetal lung during intrauterine life; therefore, only a small amount of circulating blood enters the pulmonary circulation during development. During normal transition of a term infant from intrauterine to postnatal life, this ductus closes between 24-96 hours of life as there is a decrease in pulmonary vascular resistance, smooth muscle constriction, decreased production of prostacyclin and prostaglandin I<sub>2</sub>, increased production of endothelin 1, and an increase in acetylcholine and bradykinin (Toyer & Fox, 2004). In addition, there are constricting properties of oxygen and an increase in this gas helps to constrict the ductus and begin apoptosis or cell death.

The incidence of a persisting PDA can range from 10-60% of neonates inversely related to gestational age and birth weight (Dani et al., 2000). In the premature infant, this closure may be delayed or non-existent for many reasons. For instance, it can be that the pulmonary resistance does not decrease enough due to the premature infants lack surfactant, the production and/or secretion of hormones is not adequate to sustain ductal closure, or that premature neonates are less sensitive to the constricting properties of oxygen and more sensitive to the dilating properties of prostaglandins that remain in the circulation. When the DA does not close postnatally, it produces left to right shunting of the blood as mentioned above due to the increase in systemic pressure and decrease in pulmonary vascular resistance (Linder et al., 2010). This means the blood flowing from the left ventricle to the systemic circulation via the aorta, shunts across the patent ductus arteriosus back into the pulmonary circulation. This shunting results in increase pulmonary blood flow and decreased systemic blood flow; therefore, less blood flow to other vital organs. This can create very serious complications including, but not limited to,

pulmonary congestion, renal dysfunction, intraventricular hemorrhage (IVH), and gastrointestinal perforation resulting in necrotizing enterocolitis (NEC) (Heyman, 2003). The figure below allows a visualization of where this shunting takes place.

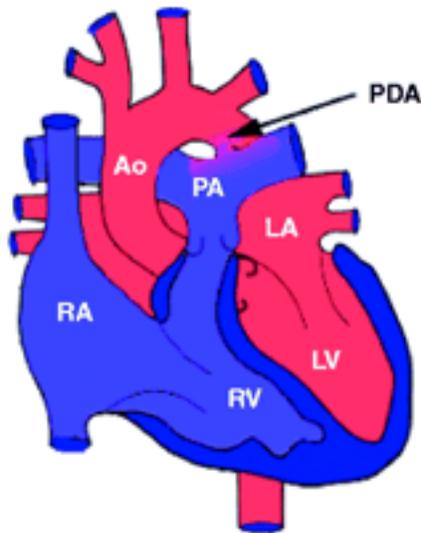


Fig. 1. Murphy, P.J. (2011). The Fetal Circulation

### Review of Evidenced-Based Literature

The databases used within the St. Catherine University Library website were: CINAHL, Medline, Cochrane review, and Google scholar. Within these databases, the keywords: ibuprofen, neonatal population, and patent ductus arteriosus (PDA) were used. The timeframe used in the search was 2000-2011. Five single studies and two meta-analysis were chosen to be analyzed which compared indomethacin to ibuprofen in terms of their efficacy and adverse effects.

The five single center studies reviewed all had similar purposes. They were to compare the efficacy and safety of ibuprofen versus indomethacin in the treatment of the PDA in a neonate. The efficacy was determined by whether or not the PDA closed with the appointed treatment. Safety referred to the side effects or complications seen as a result of taking a

particular medication. Within the five articles being used to investigate this topic, two different research designs were seen. Three studies used randomized control trials (RCTs) and examined the outcomes prospectively (Lago et al., 2002; Overmeire et al., 2000; Su et al., 2007), and two used retrospective comparative studies (Katakam et al., 2007; Linder et al., 2010). RCTs are considered an experimental design, which is the strongest method to examine causality. With these studies being conducted in an institution allows for more control over variables, increasing the validity of the results (Burns & Grove, 2009). The studies used random assignment, spreading out the extraneous variables, adding to the validity of the results. The retrospective comparative studies examined information in the charts of neonates whom had previously received either ibuprofen or indomethacin to measure effectiveness and safety.

Power analysis was done in all of the RCTs, making the sample sizes appropriate in order to improve the external validity, making the results generalizable (Lago et al., 2002; Overmeire et al., 2000; Su et al., 2007). In the retrospective study done by Linder et al. (2010), a power analysis was also performed validating the sample size, but it was not mentioned to have been done in the study conducted by Katakam et al. (2007). By using inclusion and exclusion criteria along with random assignment increases the strength of the sampling strategy and generalizability of the findings.

The independent variables or treatment in these studies are the medications: indomethacin and ibuprofen. In all of the studies, the closure of the PDA was the primary dependent variable of concern. Adverse effects and morbidities became additional dependent variables analyzed. Some of the most frequent adverse effects seen were: decreased renal function, thrombocytopenia, increase in intraventricular hemorrhage (IVH), necrotizing enterocolitis (NEC), bronchopulmonary dysplasia (BPD), sepsis, increase length of stay, and

death. The three RCTs used the same standard dosing amounts and schedules with each medication. Using the same type, amount, and frequency of medication increases the validity and generalizability of the results. All five studies used the same type of strategies to measure particular outcomes. For example, they all used echocardiography to monitor the PDA, lab values to monitor renal function, thrombocytopenia, etc., and cranial ultrasounds to monitor for IVH, and so on. This makes all of the study results very comparable.

In the five single center studies conducted, there was no statistical significance in the closure of the PDA after receiving ibuprofen versus indomethacin. However, in all of the literature, excluding the study conducted by Linder et al. (2010), there were statistically significant renal effects. These studies found that indomethacin produced an increased incidence of oliguria ( $p = 0.017$ -  $p=0.13$ ) and an increase in serum creatinine ( $p= 0.03$  -  $p= 0.04$ ). In the study by Linder et al. (2010), indomethacin was also found to produce a statistically significant increase in thrombocytopenia ( $p < 0.007$ ). All other outcomes analyzed such as NEC, IVH, BPD, and mortality rates were found to be non-significant.

After the five smaller studies were reviewed, two larger meta-analysis were reviewed. One analysis was by Thomas et al. (2004) comparing ibuprofen and indomethacin for the closure of the patent ductus arteriosus and the other analysis was a Cochrane review published by Ohlsson et al (2010) looking at “ibuprofen for the treatment of the patent ductus arteriosus in preterm and/or low birth weight infants.” The first analysis was a compilation of nine studies, which found similar results of the previous single center studies. That being that there was no statistical significant between the two medication for closing the PDA; however, there is statistically significant results in adverse effects as previously mentioned (Thomas et al., 2004). Five of these nine trials found a statistically significant increase in serum creatinine

concentration ( $p < 0.001$ ), and statistically significant decreased urine output levels in the indomethacin group ( $p < 0.001$ ). This study also examined chronic lung disease as defined by neonates requiring oxygen after 28 days postnatally and found this to be a more common finding in the ibuprofen group ( $p < 0.05$ ) (Thomas et al., 2004). In this study, other adverse outcomes such as necrotizing enterocolitis, intraventricular hemorrhage, sepsis, retinopathy of prematurity, periventricular leukomalacia, and re-opening of the PDA were not found to be statistically significant.

The Cochrane Collaboration meta-analysis conducted by Ohlsson et al. (2010) also compiled results from twenty different studies. One of these studies compared ibuprofen to a placebo and not indomethacin, so these results will not be included. The criteria for these studies were based on the type of study (randomized or quasi-randomized controlled trials), and the age or weight of the participants (preterm infants  $< 37$  weeks gestation or low birth weight of  $< 2500$  grams) with a PDA confirmed by echocardiogram. Once again, there were no statistically significant differences in the findings with regards to the closure of the PDA, mortality, need for surgical ligation, reopening of the ductus, ROP, IVH, sepsis, or length of hospital stay. There was; however, statistical significance with regards to the incidence of decreased urine output in the indomethacin group ( $p = 0.006$ ) and increase in serum creatinine ( $p < 0.01 - p = 0.07$ ).

### **Implications for Practice**

The effects of a patent ductus arteriosus on a neonate can range from mild to severe effects. The most likely event to occur if the ductus does not close on its own or with the help of a prostaglandin inhibiting medication or surgical ligation is that the pulmonary blood flow will become too much for the neonate to handle leading to a back up of blood into the heart creating

congestive heart failure (CHF) (Avery, 2005). Once the baby has CHF, this can lead to numerous other complications and morbidities.

The medical implications to discuss are the two statistically significant findings when using indomethacin instead of ibuprofen and those are decreased urine output (oliguria) and increased serum creatinine. Decreased urine output can be a result of decreased renal blood flow, acute tubular necrosis, and/or nephron dysgenesis (Avery, 2005). These are all negative effects on the renal system and could potentially create permanent renal damage. The other negative effect, which was statistically significant, was an increase in serum creatinine. Serum creatinine is used as a measure of the glomerular filtration rate (GFR) in the neonate. GFR is a function of the kidney that correlates well with the gestational age of the child. This means the lower the gestation, the lower the GFR and visa versa. Giving indomethacin to preterm children with premature glomerular filtration rates places the neonate at a disadvantage and can lead to decreased urine output and decreased filtration of other substances of which would accumulate and become nephrotoxic.

### **Parent Education**

Parent education would be vital regarding the disease process, the available therapies, and potential adverse reactions in all scenarios. The first topic of discussion would be regarding what a PDA is and why it is required during fetal life, but how it can create additional illnesses and complications if the ductus does not close postnatally. Then, it would be important to support why there is a preference to first trial a medication versus the ligation even when there is not a guarantee of ductal closure and there are additional risks of side effects when giving the medication. The next important discussion would be regarding what medication will be used and

why it is the preferred medication to a particular facility or providing practitioner. Then with any medication being given, it would be important to discuss the potential adverse effects, which could occur. After supporting a medication and thoroughly discussing the reasons behind giving it, it is also important to discuss the possibility of needing the surgical ligation if the medication did not produce the intended outcome.

### **Conclusion**

There is sufficient evidence within the five individual studies and the two meta-analysis reviewed that substantiate the results that the two medications have similar outcomes with regards to closing the PDA. However, there are statistically significant side effects, particularly effecting renal function when given indomethacin. This side effect alone is a strong argument for a change in practice especially considering the population being neonates with already fragile, immature systems. Given how ibuprofen produces less adverse effects, while producing similar ductal closure results, is a clinical indication that it should be used in place of indomethacin. Knowing that facilities throughout the country continue to use indomethacin over ibuprofen when the two medications have comparable outcomes with ibuprofen producing fewer side effects is why this topic should be researched more extensively. Providing these statistics and findings will be important in order to promote change in a field that cares for some of the most delicate patients.

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