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Effect of Oral Ibuprofen and Oral Acetaminophen in the Treatment of Symptomatic Patient Ductus Arteriosus in Premature Infants

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Abstract

Background: Patency of the ductus arteriosus (PDA) is a prevalent condition in preterm neonates with respiratory distress syndrome (RDS), and 60 percent to 70 percent of preterm children born at 28 weeks have PDA treatment, either medically or surgically. **Subjects and Methods:** All preterm children delivered at Career Institute of Medical Sciences & Hospital with a PDA and a diagnostic age of less than 14 days were included in the study. All preterm children were checked for oxygen dependency; increased PCO2, heart murmur, heart failure symptoms, Bounding Pulse, and suspicion of PDA, echocardiography was performed on them. They enrolled in the trial if the condition was confirmed. After gaining parental consent, a total of 56 children with PDA were enrolled in the trial and were randomly assigned to one of two groups. **Result:** The ductus arteriosus was entirely closed in all 5 infants treated with acetaminophen and 5 of the 7 infants treated with ibuprofen who received the second round of treatment (P=0.12). According to the findings, there was no statistically significant difference between the side effects of the two prescription drugs, acetaminophen and ibuprofen (P=0.36). **Conclusion:** Oral Ibuprofen can effectively seal PDA, but it is regrettably linked with some side effects, limiting its utility. As a result, we investigated an alternate medicine with similar efficacy, less side effects, and fewer contraindications. Because Ibuprofen and Acetaminophen have similar efficacy and Acetaminophen has a higher safety profile, it is recommended that Acetaminophen be used first.

Key Words: Acetaminophen, Ibuprofen, PDA and NICU.

INTRODUCTION

Patency of the ductus arteriosus (PDA) is a common problem in preterm newborns with respiratory distress syndrome (RDS), and 60 percent to 70 percent of preterm children born at 28 weeks undergo medicinal or surgical treatment for a PDA.[1,2] Neonates that have a left-to-right shunt via the ductus aggravating their RDS have a higher likelihood of respiratory failure, a worse survival rate, and a higher risk of intracranial haemorrhage (ICH), chronic lung disease (CLD), and necrotizing enterocolitis (NEC).[3] As a result, before a major left-to-right shunting occurs, PDA should be closed. The functional closure of the ductus arteriosus in neonates occurs within the first few hours of birth, and essentially little blood passes through the duct in any babies born after 96 hours.[4] Closure of the ductus after delivery occurs for a variety of reasons, but it has been demonstrated that a rise in arterial oxygen pressure, which occurs after birth along with the ventilation of the lungs, causes the duct to close.[5] In the meantime, prostaglandins play an important part in duct patency, and the balance between the effects of oxygen retractor and prostaglandins vasodilator is critical. The effects of these materials, on the other hand, are dependent on the gestational age of babies; in preterm infants, the ductus sensitivity is more sensitive to the effects of patancy owing to prostaglandins, and this sensitivity decreases with age.[6] Patent ductus arteriosus (PDA) affects 50% of newborns born before the 28th week of pregnancy. Most doctors prefer to address this condition in babies, however some specialists believe that treatment is unnecessary in this circumstance.[7] The patent ductus arteriosus has a number of hemodynamic effects, including increased pulmonary circulation, which is linked to an increased risk of respiratory failure, pulmonary edoema and decreased alveolar development in chronic lung illness, and systemic hypoperfusion.[8] The patent ductus arteriosus can also impair brain and tissue oxygenation, putting kids at risk for neurological disorders.[9] Surgical urethral blockage or pharmacological therapy with cyclooxygenase inhibitors are the most common treatments for patent ductus arteriosus. Previous study has identified certain undesirable and dangerous side effects of surgical treatment, including pneumothorax, chylothorax, and infection. Paralysis of the vocal cords and its impact on feeding and respiratory issues have also been observed in more than 40% of instances.[10] Recent research has proven the link between surgically closing a patent ductus arteriosus and neurological developmental abnormalities, persistent pulmonary illness, and serious retinopathy in preterm babies.[11] Furthermore, in certain circumstances, surgery to close a patent ductus arteriosus has failed to improve the clinical state of infants with the disorder. Closing it with medication, on the other hand, can avoid alveolar development abnormalities.[12] In most countries, two types of cyclooxygenase inhibitors are used to treat a patent ductus arteriosus. Indomethacin and ibuprofen lysine are two examples. The success rate of patent ductus arteriosus closure is the same for both medications when the regular dose is used.[13] The true response in extremely low birth weight newborns is predicted to be between 40 and 60%, while the figure in older infants is over 80%.[14] The patancy of the ductus, on the other hand, may recur in 20% of treated neonates. Also, if a baby is older than 10 days, their responsiveness is reduced. The poor rate of closure of the patent ductus arteriosus in very low birth weight neonates is

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due to differences in the pharmacokinetics of the two medications, not pharmacodynamic differences.[15] Both of these medications have a strong impact on the closure of patent ductus arteriosus, and their optimal dose can be permanent in more than 90% of preterm newborns. The most significant difference between these two medicines is their toxicity. These have two types of side effects: reversible short-term effects (such decreased organ perfusion and renal function) and long-term consequences (like decreased organ perfusion and kidney function) (such as chronic lung disease and the destruction of nerve growth). When comparing the short-term adverse effects of these medicines, ibuprofen outperforms indomethacin. However, considering the potential side effects of these two treatments, as well as the high number of situations where they are contraindicated, finding a safe and effective alternative therapy appears to be important.

METHODS

From November, 2015 to October, 2016, this study was conducted in the Department of Neonatal Intensive Care Unit (NICU) of Career Institute of Medical Sciences & Hospital in Lucknow, Uttar Pradesh. All preterm children delivered at Career Institute of Medical Sciences & Hospital with a PDA and a diagnostic age of less than 14 days were included in the study. All preterm children were checked for oxygen dependency; increased PCO2, heart murmur, heart failure symptoms, Bounding Pulse, and suspicion of PDA, echocardiography was performed on them. They enrolled in the trial if the condition was confirmed. After gaining parental consent, a total of 56 children with PDA were enrolled in the trial and were randomly assigned to one of two groups:

Group-1: was assessed for two days and given acetaminophen at a dose of 15 mg/kg/6h (8 doses).

Group-2: received ibuprofen at a dose of 10 mg / kg / stat, followed by two doses of 5 mg / kg / 12h.

Patients were re-echocardiographed at the end of the three-day therapy session. If each patient's echocardiographic findings indicated a lack of ductus arteriosus closure, the medicine was given to them for a longer amount of time, and they were re-echoed at the end of the third day. Patients who did not react to two courses of medication treatment were chosen as surgical candidates. Patients were monitored for side effects during the therapy period, with a review of their 24-hour urine output, any blood, serum bilirubin, and creatinine levels. Data was examined with the use of independent t-tests (in the case of normal distribution of data) or Mann-Whitney tests (in the event of nonnormal distribution of data) and chi-square tests using the statistical programme SPSS 16.

RESULTS

The participants in this study were 56 preterm infants with PDA who were born at Career Institute of Medical Sciences & Hospital. Patients were given acetaminophen in 51.8 percent (n = 29) of cases and ibuprofen in 48.2 percent (n=27 cases). At birth, the average age of the neonates was 4.51±1.2 weeks. Both groups had significant differences in the mean age of their infants (P= 0.52). Males accounted for 30 percent (53.6 percent) of infants, while females accounted for 26 percent (46.4 percent). The sex frequency of babies in both groups did not differ significantly (P=0.62). Ibuprofen-treated infants weighed 816±1552 g on average, while acetaminophen-treated infants weighed 887±1665 g on average (P=0.57). Table 1 shows that at the end of the first period, 20 (74.1%) of infants treated with ibuprofen and 24 (82.8%) of infants treated with acetaminophen had recovered, while the rest were treated with another treatment period. Of course, the difference of 4.9 percent was not statistically significant (P=0.24), according to the findings of the chi-square test.

The closure of PDA in neonates has been indicated in Table 2 by their groups at the end of the first period of their treatment. As shown in the table, there was no change in the position of patent ductus arteriosus at the end of the first period of therapy in 2 (7.4%) of the cases treated with ibuprofen and 1 (3.4%) of the cases treated with acetaminophen (P=0.16).

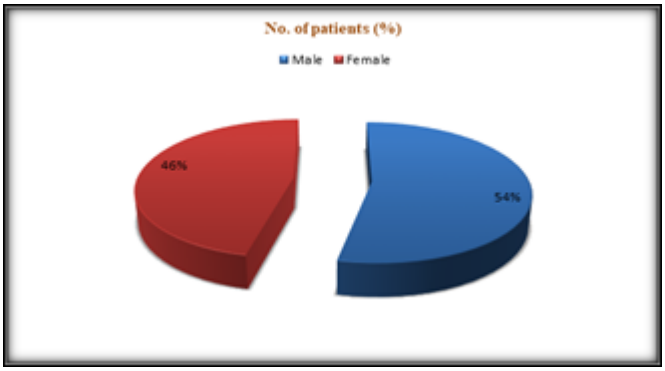

Figure 1: Shows the distribution of gender.

Table 1: The number of treatment periods for newborns with PDA are distributed according to the type of treatment they received.

Group	Treatments	Treatment Periods		Total
		One period	Two periods	
Group-1	Acetaminophen	24(82.8%)	5(17.2%)	29(51.8%)
Group-2	Ibuprofen	20 (74.1%)	7 (25.9%)	27 (48.2%)
Total		44 (78.6%)	12 (21.6%)	56 (100.0%)

Table 2: Closure of PDA in newborns by type of treatment at the completion of the first period.

Group	Treatments	PDA at the end of first period			Total
		Perfect	Imperfect	Unchanged	
Group-1	Acetaminophen	24 (82.8%)	4 (13.8%)	1 (3.4%)	29 (51.8%)
Group-2	Ibuprofen	20 (74.1%)	5 (18.5%)	2 (7.4%)	27 (48.2%)
Total		44 (78.6%)	9 (16.1%)	3 (5.4%)	56 (100.0%)

Table 3: Closure of PDA in newborns by type of treatment at the completion of the second period.

Group	Treatments	PDA at the end of second period			Total
		Perfect	Imperfect	Unchanged	
Group-1	Acetaminophen	5 (100.0%)	0	0	5 (41.7%)
Group-2	Ibuprofen	5 (71.4%)	1 (14.3%)	1 (14.3%)	7 (58.3%)
Total		10 (83.3%)	1 (8.3%)	1 (8.3%)	12 (100.0%)

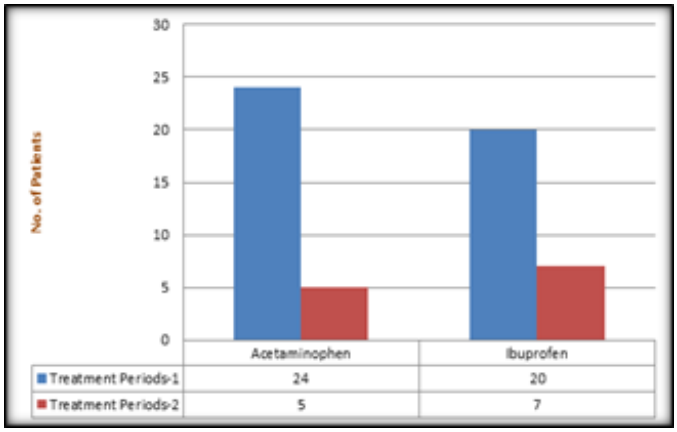

Figure 2: Distribution of the number of treatment periods of infants with PDA by the type of treatment received.

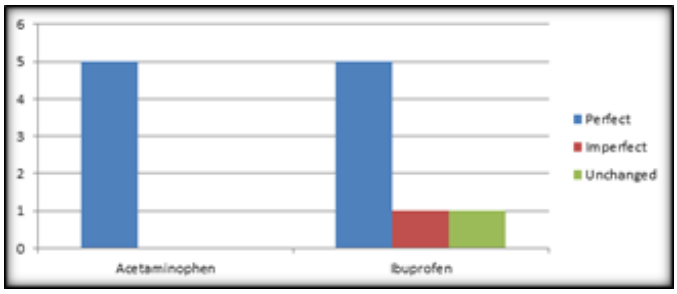

Figure 3: Closure of PDA in babies at the end of the second period by the type of treatment received.

[Table 3] demonstrates that the ductus arteriosus was entirely closed in all 5 infants treated with acetaminophen and 5 of the 7 infants treated with ibuprofen who received the second round of treatment (P=0.12). According to the findings, there was no statistically significant difference between the side effects of the two prescription drugs, acetaminophen and ibuprofen (P=0.36).

DISCUSSION

According to the findings of a recent study, the effects of oral acetaminophen on the closure of the PDA are comparable to those of ibuprofen, and both of them are effective on the closure of the PDA in preterm newborns to the same amount. In addition, there was no difference in the number of problems associated with the use of these medications in the treatment of this group of babies. Most neonates' ductus arteriosus will be effectively closed on the first day of life, and patent ductus arteriosus for permanent (PDA) is abnormal. Because patent ductus arteriosus occurs in 30-60% of infants with very low birth weight, and their own permanent closure of the ductus occurs in only one third of infants with less than 1000 grammes in the first four days of life, the overwhelming majority of these infants are potential candidates for medical or surgical interventions.[16] As a result, one of the most important issues in baby science is patent ductus arteriosus closure procedures. Although popular medical procedures such as indomethacin and ibuprofen are used, the side effects and difficulties in using them have always piqued professionals' curiosity in developing novel approaches with less drawbacks. There have been few studies testing the effectiveness of acetaminophen in the treatment of patent ductus arteriosus and comparing it to other medications. Contraindications are utilised in circumstances when COX inhibitors are ineffective because acetaminophen is inefficient as a supplement, not as a first-line treatment. There was no significant difference in the efficacy of oral ibuprofen and oral acetaminophen on the closure of the PDA in preterm infants in this trial. Dang et al,[17] conducted a randomised controlled trial on 160 preterm infants (gestational age less than 34 weeks) to compare the efficacy and safety of oral ibuprofen versus oral acetaminophen in the treatment of patent ductus arteriosus. The results showed that both drugs were equally effective in the treatment of patent ductus arteriosus. These findings are in line with what we found in our research. The results of a study comparing the effectiveness and safety of oral acetaminophen vs. oral ibuprofen for the treatment of patent ductus arteriosus in 90 premature infants with a gestational age less than 30 weeks and a birth weight less than 1250 g showed that after the first course of treatment, 77.5 percent of babies receiving acetaminophen had their patent ductus arteriosus closed. Oral acetaminophen, according to the researchers, can be a useful alternative for the treatment of patent ductus arteriosus in premature newborns.[18] In comparison to ibuprofen, acetaminophen can be considered a safe and promising medicine for the treatment of patent ductus arteriosus in premature newborns, according to Sinha et al,[19] and Terrin et al.[20] Yurttutan et al,[21] who assessed and treated six premature infants with patent ductus arteriosus with oral acetaminophen, concluded that acetaminophen can be considered a main option for the management of patent ductus arteriosus in these infants due to its low side effects, low cost, and effectiveness. This result is in line with what we discovered during our investigation. According to the current findings, while the incidence of ibuprofen-treated infants is 8.6% higher than the acetaminophen group, this difference was not statistically significant, contrary to a recent study premise.

According to a study conducted by Dang et al.[17] to compare the efficacy and safety of oral ibuprofen versus oral acetaminophen in 160 preterm infants (gestational age less than 34 weeks), hyperbilirubinemia or gastrointestinal bleeding were slightly lower in the acetaminophen group than in the ibuprofen group. However, no significant variations in side effects or other difficulties were found between the two groups in this study. According to the findings of Sinha et al,[19] unlike the prescription ibuprofen, which had many side effects, no side effects were seen following administration of oral acetaminophen. Despite the fact that therapy with ibuprofen or indomethacin had a lot of side effects, Terrin et al,[20] found that treatment with acetaminophen had no adverse responses or major issues. Unlike the findings of a recent study, the data of the studies above imply that ibuprofen has a higher prevalence of adverse effects than acetaminophen. Despite the high prevalence of problems among infants treated with ibuprofen, there appear to be no significant differences in the current investigation, which is likely owing to the small number of samples examined.

CONCLUSION

These studies show that oral Ibuprofen can effectively seal PDA, but it is regrettably linked with some side effects, limiting its utility. As a result, we investigated an alternate medicine with similar efficacy, less side effects, and fewer contraindications. Because Ibuprofen and Acetaminophen have similar efficacy and Acetaminophen has a higher safety profile, it is recommended that Acetaminophen be used first. Despite the fact that we have shown that acetaminophen can be used as the treatment of choice for PDA in preterm newborns with acceptable efficacy, more research is needed.

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