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Original Research Article

Comparison of Efficacy of Paracetamol and Ibuprofen for Treatment of Hemodynamically Significant Patent Ductus Arteriosus in Preterm Infants

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Abstract:

Background: For the pharmaceutical closure of hemodynamically significant patent ductus arteriosus (hsPDA) in preterm newborns, indomethacin and ibuprofen (IBU) have been approved. Although recent studies have shown that paracetamol (PCM) can also be utilized, more investigation is needed to determine its safety and effectiveness. The objective is to evaluate the safety and effectiveness of PCM and IBU in treating hsPDA in preterm newborns.

Methods: With parental approval, an observational study was designed. Patients' hsPDA was assessed based on 2D echo results and clinical observations. Following the establishment of inclusion and exclusion criteria, a 3-day course was provided to 100 patients who were then assigned to either PCM or IBU. If necessary, a second round of the same medication was administered following echocardiographic and clinical examination. The rate of ductal closure, medication safety, and adverse events served as the outcome measures.

Results: 76.25% was the closure rate for the PCM group and 75% for the IBU group. In the first course, IBU had a much greater closure rate (45% vs. 16.25%). For PCM and IBU, the observed mean closure times were 4.54 days and 4 days, respectively. In the low-birth-weight group and in cases when platelet levels were below normal, PCM provided a greater closure rate. There was no discernible difference between the groups in terms of safety either.

Conclusion: PCM is a superior option for individuals with low platelet counts and comorbidities, and it can be recommended as a first-line treatment for hsPDA cases in preterm newborns.

Keywords: Hemodynamically Significant Patent Ductus Arteriosus, Ibuprofen, Paracetamol, Platelet Count, Preterm Infants.

Introduction

Incidence of patent ductus arteriosus (PDA) is particularly high in preterm newborns ranging from 20% to 60% [1]. Because of immaturity, there is a lack of a normal closure mechanism, which is the reason for the increase in occurrence. Also, there is a strong correlation between PDA closure and gestational age and birth weight. Eighty percent of newborns weighing less than 1200 grams have PDA. It rises to 40% in infants weighing less than 2000 g [2]. Another study reveals that 48% of newborns weighing less than 1000 grams have symptomatic PDA [3]. Furthermore, PDA is seen in 80% of babies with respiratory distress syndrome (RDS) [4].

Hemodynamically significant PDA (hsPDA) is associated with severe morbidity and mortality. It comprises bronchopulmonary dysplasia (BPD), retinopathy of prematurity (ROP), necrotizing enterocolitis (NEC), and intraventricular hemorrhage (IVH). The smooth muscle fibers that make up the ductus arteriosus (DA) are layered in a spiral and longitudinal fashion, encircled by concentric layers of elastic tissue. The medial smooth muscle fiber contracts as a result of breathing in air that is high in oxygen after birth. This causes the lumen to constrict and the DA length to shorten, starting at the pulmonary end and continuing until functional closure occurs in a matter of hours or days [5]. Smooth muscle atrophy and the development of medial and intimal connective tissue signal the beginning of the second stage of closure. This in turn leads to a lamentation and non-contractile structure over the next 3 weeks.

Though the precise process of DA closure is yet unknown, prostaglandins produced by the cyclooxygenase enzymes cox1 (ptgs1) and cox2 (ptgs2) are important mediators of both DA

patency and closure. It is well known that the cox product prostacyclin PGI2 and PGE2 are DA vasodilators. The COX-2 expression in the DA of premature offspring is reported to increase with advancing gestation and afterbirth, indicating that COX-2 expression inhibited the infant's post-natal constriction [6]. Prostaglandins function by means of a group of G Protein receptors. The receptors in the E P family are significant. It seems that the EP4 subtype is crucial [7]. Contrary to closely similar NSAIDs, paracetamol interferes with COX isoenzyme peroxidase activity, primarily with COX2. This is especially true when arachidonic acid and peroxides are low in the cellular milieu. Given that COX2 is constitutively produced in neural tissue and looks ineffectual in inflammatory tissue, this helps to explain PCM's apparent central impact [8].

Since indomethacin was first used in 1976, a large body of research and published articles has been produced regarding the therapy of PDA in preterm newborns. As of right now, the FDA has approved IBU (ibuprofen and indomethacin) for the pharmacological closure of PDA. Over time, the use of indomethacin has decreased due to its negative effects, and it has mainly been replaced by IBU. Even after that, there is still debate and discussion about it. Although PCM has recently been tested for PDA, the FDA has not yet approved its usage for it.

In order to compare PCM with IBU for the treatment of hsPDA in terms of drug safety, long-term outcome, and closure %, more research is necessary. The current study is intended to take place in this particular situation. The aims are to compare the efficacy and safety of PCM and IBU for the treatment of hsPDA in preterm newborns. The study also focuses on the numerous prenatal and postnatal factors that may affect pharmaceutical closure and also other comorbidities linked with PDA.

Material and Methods

This observational study was conducted at Department of Pediatrics, Darbhanga Medical College and Hospital, Laheriasarai, Bihar from September 2021 to August 2023. Consent from the parents was acquired. We looked at premature infants with PDA who were admitted to the NICU. On the basis of clinical and echocardiographic data, patients were assessed for hsPDA.

In the event that pharmacological closure was chosen, the subjects underwent screening for inclusion and exclusion criteria and were thereafter assigned to either oral or intravenous PCM or oral IBU. Two groups each received 100 cases which were analyzed consecutively. On the basis of the clinical history and 2 D echocardiographic results, operational definitions of hsPDA were created. Moreover, outcome measures were specified. Oral/IV PCM (15 mg/kg every 6 hours) is administered to infants for three days, or oral IBU (10 mg/kg initially, then 5 mg/kg every 24 and 48 hours) is administered. The choice of PCM or IBU treatment was based on the specific characteristics of each patient, including platelets, creatinine, serum bilirubin level, and comorbidities that were present. Echocardiography results following the initial course of treatment determine whether a patient received a second course of treatment. No additional treatment was administered if, following two treatments, there was only mild ductal shunting and no need for respiratory assistance.

Patients who did not respond to treatment were assessed, and if they were suitable for rescue medication, a third course of treatment using the alternative drug was attempted. After undergoing a second evaluation, the patient was recommended for surgery or catheter ligation if clinical treatment was not feasible. Throughout the course of the treatment, drug safety variables such as 24-hour urine output, bleeding propensity, IVH grade, and serum creatinine and bilirubin levels were evaluated every day. In addition, an eye check was performed four weeks postpartum. Treatment was stopped if any of the following conditions developed: gastrointestinal bleeding, renal failure, NEC, IVH grade 3-5, and IVH.

The rates of ductal closure following treatment and the patient's improvement hemodynamically that is, weaning off ventilator support and having a lower oxygen requirement were the primary end measures. Investigations revealed that the patient's CBC, RFT, and LFT values returned to normal. Throughout the course of treatment, echocardiography was used to monitor each infant daily.

Secondary results, such as the safety of both medications, as well as early and late adverse effects, such as periventricular leukomalacia (PVL), NEC, sepsis, death, oliguria, tendency to bleed, and hyperbilirubinemia, will be examined in both groups. The term "early adverse events" was used to describe side effects that happened during and up to a week after the medication was administered.

Among the patients included were those with an echocardiographic diagnosis of hsPDA, a gestational age of ≤34 weeks, and a postnatal age of ≤14 days. Major congenital abnormalities, infants older than 34 weeks GA, and congenital cardiac disease requiring PDA to maintain blood flow were eliminated from this study.

MS Excel was used to gather, tabulate, and perform statistical analysis on all pertinent data. Utilizing the Chi-square test for categorical variables, the t test for continuous variables, and the z test for

proportions, comparisons were made. Using online software, a logistic regression analysis was carried out. The threshold of $p \leq 0.05$ was deemed statistically significant.

Results: Patients who met the inclusion and exclusion requirements underwent clinical evaluations for PCM and IBU therapy. PCM was administered to patients with GI bleeding, sepsis, hyperbilirubinemia, oliguria, and platelet counts < 95000. Of the 100 patients, 80 were put on PCM, while 20 were put on IBU. The study's overall closure rate was 76%. The closure rates for the PCM group were 76.25% and the IBU group was 75%. Table 1 presents the findings.

Table 1: Treatment outcome

Medication	Closed	Closed (%)	Referred	Referred (%)	Death	Death (%)	Total
Paracetamol	61	76.25%	1	1.25%	18	22.5%	80
Ibuprofen	15	0.75%	1	6.67%	4	26.67%	20
Total	76	76.0%	2	2%	22	22.0%	100

Between the groups, there was no discernible difference (p=1.0931). Table 2 provides the overall treatment outcome for PDA closure following the first and second course of treatment. According to the results, IBU had a far higher first-course closure rate (45% vs. 16.25%).

Table 2: Closure rate in the first and second course

Medication	Closed in first course (%)	Closed in second course (%)
Paracetamol	16.25%	71.6%
Ibuprofen	45.0%	54.5%

The findings indicate that in order to improve closure rates, PCM need to be treated for a longer amount of time.

Analysis was done on the treatment outcomes according to birth weight and gestational age. Studies were also conducted on comparisons between PCM and IBU in various GA groups and BW. As predicted, it was seen that the closure rate rose with gestational age.

When comparing these parameters across the PCM and IBU groups, a similar pattern was not seen with regard to body weight, where the maximum closure was noted in the birth weight group weighing more than 2.5 kg. The results are shown in Fig. 1.

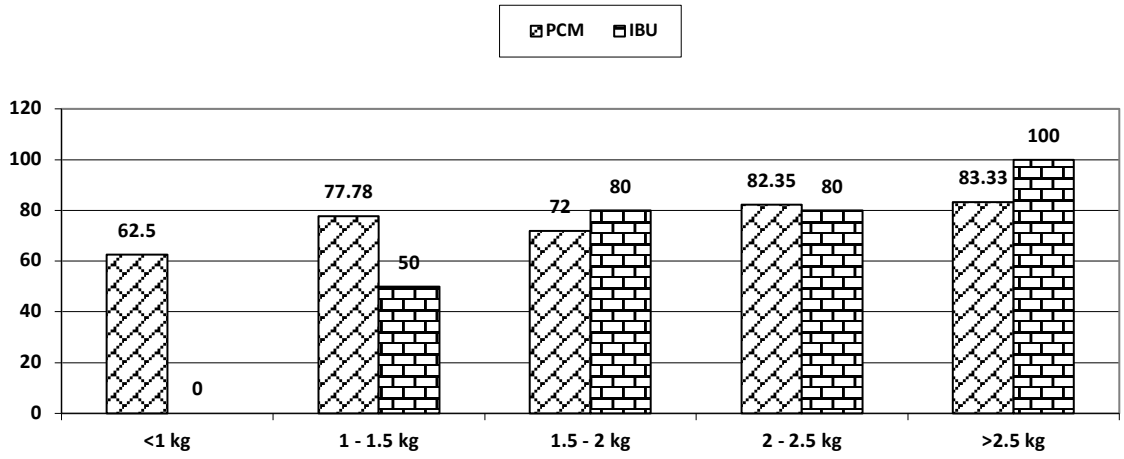

Figure 1: PDA Closure rate with PCM and IBU based on birth weight

We performed statistical analysis on the effects of different parameters on PDA closure. Using antenatal steroids (p=0.78), mechanical ventilation support (p=0.87), starting medication earlier than seven days (p=0.61), RDS (p=0.87), gestational age before thirty weeks (p=0.47), PDA size (≤3 mm versus >3 mm (p=0.97), La/Ao ratio (≤3 versus >3 (p=0.98), and platelet count were the parameters.

With the exception of platelet count, all metrics demonstrated statistical significance across groups. The outcome was compared between pre-treatment values of less than 150,000 and more than 150,000 in terms of platelet count. A significant difference between the groups was discovered (p=0.0004). Pre-treatment platelet counts <150,000 demonstrated a higher closure rate. Up to 150,000 platelet counts were found to have a positive link with PCM on logistic regression, according to further research (p=0.06). There was no association seen above 150,000 (p=0.4).

The PCM group had 80 patients, of which 14 had a history of early-onset sepsis (EOS), 11 had newborn jaundice (NJ), and 22 had creatinine values greater than 1 mg/dL.

The study's closure percentages were 85.7 %, 68.18%, and 85.7%, respectively. In the IBU group, the corresponding closure percentages were 71.43%, 66%, and 80%, in that order. When PCM and IBU's platelet pre-treatment and post treatment values were examined, no statistically significant differences were found.

The study found that the average amount of time needed for closure was 4.43 days. A small variation was noted throughout this time frame between the groups. IBU had four days and PCM had 4.54 days.

The mean time of the introduction of medication in the study was 3.62 days of age. PDA had a mean diameter of 2.68 mm. In this study, a mean LA/AO ratio of 2.19 was found. Pre- and post-treatment values of platelets, creatinine, urea, and bilirubin were obtained and statistically compared with respect to the safety parameters of the two medicines. There were no discernible variations between the pre- and post-treatment values of any of the parameters. Pre- and post-treatment mean bilirubin readings increased in the PCM group (7.812 compared 10.986), although this difference was not statistically significant (p=0.0885). The IBU group did not exhibit this variation. Table 3 presents the results.

Table 3: Comparison of pre-treatment and post-treatment values of various parameters (t-test)

Parameters	PCM			IBU		
	Mean value before treatment	Mean value after treatment	p-value	Mean value before treatment	Mean value after treatment	p-value
Platelet	151286	141190	0.508	220500	190500	0.4004
Creatinine	0.55	0.595	0.7861	0.984	0.894	0.3287
Urea	29.15	28.55	0.6871	53.6	45.56	0.5317
Bilirubin	7.812	10.986	0.0885	10.33	8.77	0.5482

The findings demonstrated that there was no difference in safety outcomes between PCM and IBU when it came to treating hsPDA. The development of NEC, EOS, LOS, hypocalcemia, hyponatremia, BPD, IVH, gastrointestinal bleeding, etc. was assessed in the patients. It has been noted that newborns with hsPDA frequently have many comorbidities. In both groups, there were no reports of gastrointestinal bleeding, BPD, or IVH cases.

Functional Terminologies hsPDA: prenatal and postnatal medical history, Clinical findings include a bounding pulse and hyperactive precordium, as well as a hypotensive demand for vasopressor therapy and a persistent need for respiratory assistance. results of an echocardiogram LA/Ao ratio >1.5, PDA size >1.5 mm, absent or retrograde Clinical resolution and either no PDA or a tiny PDA (diameter <1.5 mm) are required [9].

Discussion

When compared to no intervention, it is well-established that pharmacological therapy of patent ductus arteriosus in preterm newborns is advantageous [10,11]. Yingqi et al. and Ohlsson et al. 2020 examined the efficacy of PCM in treating PDA and compared it to IBU[12,13]. They demonstrated that there were no appreciable variations between PCM and IBU.

Additionally, the PCM group was found to have hyperbilirubinemia, a decreased risk of gastrointestinal hemorrhage, and a shorter mean number of days required for closure. The same outcome is observed in additional research as well (Dang et al., 2012; Oncel et al., 2014 [14–16], Ahranjani, 2020). In a prior study, it was discovered that the first PCM therapy session resulted in 26% closure and 36% PDA size reduction. The percentages with IBU were, respectively, 48.5% and 30%. (Ahranjini and others)[14]. A primary closure rate of 56.3% with PCM and 78% with IBU was observed in another study (Dang et al.,) [15]. The first course in our trial had a decreased percentage of closure with PCM, which could have been caused by the medication selection criteria. Nonetheless, the study's overall closure rate matched that of previous investigations.

After two three-day treatment regimens, there was no discernible difference in the closure of PDA across the groups in a study by Meena et al. (2020) comparing indomethacin, IBU, and PCM [17]. Following the first course, the closure rate was 42.46% in the PCM group, 37.14% with IBU, and 22.8% with indomethacin. In the indomethacin group, the cumulative rate of PDA closure was 68%; in the IBU group, it was 77.14%; and in the PCM group, it was 71.4% (p=0.716).

Regarding the impact of birth weight, the findings, as illustrated in Fig. 1, demonstrated that PCM provided a higher closure rate in the group of low birth weight babies.

A high platelet count (181×109/L) was found to independently raise the likelihood that hsPDA would successfully close following IBU treatment (OR: 2.556, 95% CI: 1.101–5.932, p=0.029) in one

investigation. The threshold result was slightly greater than 150×109/L, which is the thrombocytopenia diagnostic standard [18].

In a study, El-Mashad et al. found that there was no thrombocytopenia following PCM treatment, but there was a significant difference in the platelet level in both the IBU and indomethacin groups after treatment [19]. We examined the impact of platelet pre-treatment values on PCM closure rate in our investigation. A favorable connection was seen up to 150×109/L. Higher platelet counts are required for the natural closure of PDAs, as was previously described [20]. Our findings might provide a predictive value for medication selection prior to treatment initiation, and PCM might be a better option if platelet count is low. Patients with EOS and NJ had a higher rate of comorbidity closure with PCM therapy. It should be mentioned that individuals with low platelet counts (less than 95000) did not get IBU.

In terms of safety, our study was consistent with other research. One study concerns bilirubin in VLBW babies with PDA, IBU therapy was related with higher bilirubin levels than indomethacin [20]. According to one study (Dang), there were no appreciable variations between the two groups' adverse events, which included BPD, PVL, NEC, sepsis, ROP, and deaths that occurred during the hospital stay starting one week after therapy [15]. Indomethacin and IBU were found to significantly enhance NEC and GI hemorrhage in a research by Meena et al.; this was not the case in the PCM group [17]. Neither the IBU group nor the PCM group reported any cases of NEC, BPD, ROP, or GI hemorrhage during our investigation. The selection of medications and their mode of administration for the treatment of hsPDA remain highly controversial. Although the oral route has the benefit of longer serum levels, it is not always feasible. IBU was administered orally in this trial, while PCM was mostly administered parenterally. Some have argued for combined medication therapy, which has been shown to be unfavorable. There may be a chance to reopen the DA, which would necessitate a longer course of therapy.

It would have been excellent to compare PCM and IBU using a randomized control experiment. Nonetheless, our study was able to clarify information in a number of highly pertinent areas. It is a truth that a sizable portion of patients were still not improving with treatment, and a thorough investigation of the underlying causes is necessary. Therefore, taking into account the experimental neurodevelopmental research in animal models, long-term outcome studies on PCM treatment in neonates are also necessary.

Conclusion

According to the current study, PCM was just as safe and successful as IBU when it came to treating hsPDA cases in preterm infants. PCM increased the low-birth-weight group's closure rate. The study also demonstrated the usefulness of PCM in situations including comorbidities and low platelet counts. Regarding the safety and effectiveness of PCM in comparison to IBU, the results were consistent with other published studies. Therefore, it was determined that PCM can be suggested as a first-line treatment for preterm newborns with hsPDA cases.

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