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ORIGINAL ARTICLE

Comparison of Efficacy of Oral Ibuprofen versus Paracetamol for PDA Closure in Preterm Neonates

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ABSTRACT

Objective: The aim of this study is to compare the efficacy of oral ibuprofen versus paracetamol for PDA closure in preterm neonates.

Study Design: Randomized Control trial

Place and Duration: The study was conducted at Neonatology department North West General Hospital, Peshawar for duration of three years from April 2018 to March 2021.

Methods: Total one hundred and fifty preterm neonates were included in this study. Patients' detailed demographics including gestational age, gender; birth and diameter were recorded after taking informed written consent from the parents. Patients were equally divided into two groups, I and II. Group I had 75 patients and received paracetamol for closure for patent ductus arteriosus and group II received oral ibuprofen for closure of PDA. Outcomes among both groups were calculated in terms of effectiveness, mortality and post-operative complications. Data was analyzed by SPSS 22.0 version.

Results: Mean gestational age of the patients in group I was 29.12±7.44 weeks and in group II mean gestational age was 30.09±4.66 weeks. 45 (65%) male in group I and in group II 40 (53.3%) were male babies. Mean ductal diameter in group I was 3.02±1.13 and in group II mean diameter was 2.98±0.16 mm. In group I cesarean birth was found in 50 (66.7%) and in group II 48 (64%) cesarean birth was found. Mean duration of closure was lower in group I 4.24±1.03 days as compared to group II 5.01±0.03 days. PDA closure rate was higher in group I 62 (82.7%) and in group II its frequency was 58 (77.3%). Re-opening of ductus was found in 6 (8%) in group I and 8 (10.7%) in group II. Adverse outcomes were renal failure, hyperbilirubinemia and gastrointestinal bleeding among both groups. Mortality rate in ibuprofen group was higher 7 (9.3%) as compared to group I 4 (5.3%).

Conclusion: We concluded in this study that the use of drug paracetamol is effective for the closure of PDA in preterm neonates as compared to oral ibuprofen with less adverse outcomes and mortality rate.

Keywords: PDA, Neonates, Paracetamol, Ibuprofen, Complications, Mortality

INTRODUCTION

Preterm newborns with respiratory distress syndrome (RDS) are more likely to develop patent ductus arteriosus (PDA), and 60–70% of those preterm infants get medicinal or surgical therapy for it [1]. A lot of people disagree on how to handle PDA properly because studies employing non-steroidal anti-inflammatory medicines (NSAIDs) for PDA closure on preterm newborns have failed to show any significant benefits [2]. There has been evidence that a prolonged left-to-right shunt through the ductus arteriosus (DA) causing RDS leads to increasing respiratory failure, a worse survival rate, an increased risk of intraventricular hemorrhage (IVH), and BPD [1-6]. As a result, closing PDA before extensive left-to-right shunting occurs is recommended.

There are now two therapy options for PDA: the first is pharmacological treatment with an NSAID; the second is surgical ligation if medical treatment fails, which should be avoided if at all feasible because of the serious problems that go along with it [7].] Indomethacin or ibuprofen are the mainstays of PDA closure medical treatment. In 70–80% of cases, both are effective in inducing ductal closure [8,9]. Although these medications might be extremely beneficial, they can also induce serious side effects such gastrointestinal perforations, acute renal failure, and blood problems. Because it has fewer side effects than indomethacin but a lower success rate, ibuprofen appears to be the treatment of choice for PDA pharmacological closure at the moment [9]. However, it does not represent the ideal drug due to its poor safety profile [9] and a 30% failure rate [10, 11].

However, there have been no conclusive randomised controlled trials using Mefenamic acid, another NSAID (non-steroidal anti-inflammatory medicine), to seal a PDA [12]. The hunt for non-surgical alternatives to Indomethacin and maybe Ibuprofen has been sparked by a variety of side effects.

While Paracetamol's influence on prostacyclin synthesis has been recognized since the late 1990s [10, 11], it was only in the current decade that it was proposed as a viable alternative medicine for PDA closure after specific data confirmed its dose-dependent effectiveness [13]. Ibuprofen operates on the cyclooxygenase enzyme, whereas paracetamol appears to act on the peroxidase component of PG-H2synthetase. Due to the fact that peroxidase is activated at a concentration of peroxide 10 times lower than cyclooxygenase, paracetamol-mediated suppression is based on decreased local levels of peroxide (as the condition with hypoxia). Paracetamol was commonly utilized to treat patients who had failed to respond to or were contraindicated for Ibuprofen, and the majority of these studies used a 15mg/kg/dose every 6 hour oral paracetamol regimen [14].

Medications such as indomethacin and ibuprofen are currently the primary line of treatment for PDA. These medications have similar ductal closure rates, ranging from 70 to 85 percent, but various contraindications and potential side effects come with them. [15,16] When pharmacological treatment fails, doctors may turn to surgery to treat preterm newborns with symptomatic PDA, but this procedure carries a significant risk of complications. [17,18] It is therefore critical to find a medicine that is both safe and effective in the treatment of PDA as soon as possible. Preterm newborns with PDA may benefit from the use of paracetamol, a common antipyretic and analgesic medicine. There are few negative effects associated with paracetamol treatment. [19] A prospective randomized controlled trial has not yet been conducted to examine the effectiveness of this treatment.

The purpose of this study is to compare the efficacy of oral ibuprofen versus paracetamol for PDA closure in preterm neonates.

MATERIAL AND METHODS

This randomized control trail was conducted at Neonatology department North West General Hospital, Peshawar for duration of three years from April 2018 to March 2021and comprised 150 preterm neonates. Patients had major congenital malformations, fetal hydrops, life-threatening infection and those who did not give written consent were excluded from this study.

Patients were equally divided into two groups, I and II. In group I oral paracetamol 15 mg/kg every 6 h for 3 days were given to neonates and 10 mg/kg followed by 5 mg/kg after 24 and 48 h oral ibuprofen was given to patients. Neonates in the ibuprofen group received the same volume of D5W for medication administration as those in the paracetamol group between doses of oral ibuprofen. The outcome of an echocardiography examination following the first treatment course determined whether or not a participant received a second session of treatment. There was no need for additional therapy if ductal shunting was only modest after two rounds without respiratory assistance. During therapy, drug safety parameters such as 24-hour urine output, bleeding tendency, IVH grade, and serum creatinine and bilirubin levels were monitored daily. Drugs were adjusted as necessary. Four weeks after the baby was born, an eye test was performed. Renal failure, NEC, IVH grade 3–4, and gastrointestinal bleeding are all conditions that would necessitate halting treatment.

Frequencies and percentages were used for categorical variables. Mean standard deviation was used. Complete date was analyzed by SPSS 22.0 version.

RESULTS

Mean gestational age of the patients in group I was 29.12±7.44 weeks and in group II mean gestational age was 30.09±4.66 weeks. 45 (65%) male in group I and in group II 40 (53.3%) were male babies. Mean ductal diameter in group I was 3.02±1.13 and in group II mean diameter was 2.98±0.16 mm. In group I cesarean birth was found in 50 (66.7%) and in group II 48 (64%) cesarean birth was found. Mean birth weight in group I was 1487.1±581.4 g and 1501.4±359.8 g in group II. (Table 1)

Table 1: Baseline characteristics of enrolled cases

Variables	Group I	Group II
Mean gestational age (weeks)	29.12±7.44	30.09±4.66
Mean ductal diameter (mm)	3.02±1.13	2.98±0.16
Mean birth weight (g)	1487.1±581.4	1501.4±359.8
Type of Delivery		
Cesarean	50 (66.7%)	48 (64%)
Normal	25 (33.3%)	27 (36%)
Gender		
Male	45 (65%)	40 (53.3%)
Female	30 (35%)	35 (46.7%)

Mean duration of closure was lower in group I 4.24±1.03 days as compared to group II 5.01±0.03 days. PDA closure rate was higher in group I 62 (82.7%) and in group II its frequency was 58 (77.3%). (Table 2)

Table 2: Comparison of effectiveness among both groups

Variables	Group I	Group II
Mean duration of closure (days)	4.24±1.03	5.01±0.03
PDA Closure		
Yes	62 (82.7%)	58 (77.3%)
No	13 (17.3%)	17 (32.7%)

Re-opening of duct was found in 6 (8%) in group I and 8 (10.7%) in group II. Adverse outcomes were renal failure, hyperbilirubinemia and gastrointestinal bleeding among both groups. (Table 3)

Table 3: Comparison of complications and adverse outcomes among both groups

Variables	Group I (n=75)	Group II (n=75)
Complications		
Re-opening of duct	6 (8%)	8 (10.7%)
renal failure	1 (1.3%)	2 (2.7%)
hyperbilirubinemia	13 (17.3%)	15 (20%)
gastrointestinal bleeding	3 (4%)	7 (9.3%)

Mortality rate in ibuprofen group was higher 7 (9.3%) as compared to group I 4 (5.3%). (Table 4)

Table 4: Comparison of mortality among both groups

Variables	Group I (n=75)	Group II (n=75)
Mortality		
Yes	4 (5.3%).	7 (9.3%)
No	71 (94.7%)	68 (90.7%)

DISCUSSION

The majority of analogous cases, including the first [20] recorded example where paracetamol was originally used to seal the ductus arteriosus, did not employ paracetamol as the treatment of choice but rather as a supplemental medication when COX inhibitors were ineffective or contraindicated. Previous studies could not support the use of paracetamol as a first-line treatment for preterm babies with PDA because they lacked significant sample sizes for the examination of efficacy and safety-related factors such as gastrointestinal bleeding, NEC, IVH, hyperbilirubinemia and death.

In this randomized control trial 150 preterm neonates were presented. Patients were equally divided into two groups. Group I received paracetamol and oral ibuprofen was given to group II. Mean gestational age of the patients in group I was 29.12±7.44 weeks and in group II mean

gestational age was 30.09±4.66 weeks. 45 (65%) male in group I and in group II 40 (53.3%) were male babies. Mean ductal diameter in group I was 3.02±1.13 and in group II mean diameter was 2.98±0.16 mm. These findings were comparable to the previous researches.[21,22] In group I cesarean birth was found in 50 (66.7%) and in group II 48 (64%) cesarean birth was found. Mean birth weight in group I was 1487.1±581.4 g and 1501.4±359.8 g in group II. Results of our study were similar to the past some studies.[23]

With reports ranging from 20% to 60% (based on study population and diagnostic criteria)[19], El Hajjar M et al. concluded that preterm neonates have a much higher incidence of PDA. However, such high data may have been derived from PDA cases among the extreme preterms that required admission to NICU's. The prevalence of PDA in preterm newborns was estimated by Hoffman JI et al. to be 55% if detected within the first 24 hours of life [24], and it may last as long as 57 out of every 100,000 live births after the second week of life due to functional followed by structural closure [25]. One in 2,000 termneonates are born with PDA, with the condition accounting for 5–10% of all congenital cardiac disease, according to Schneider DJ Met al. [26].

In current study we found that mean duration of closure was lower in group I 4.24±1.03 days as compared to group II 5.01±0.03 days. PDA closure rate was higher in group I 62 (82.7%) and in group II its frequency was 58 (77.3%). These results were comparable to the previous some studies in which paracetamol was an effective in ductus closure.[20,21,27] Preterm infants with patent ductus arteriosus were treated with i/v Paracetamol dosed at 15 mg/kg/dose, and in 10 of the 13 patients (76.9%), the PDA was closed by the median second day after intravenous paracetamol therapy, according to Tekgunduz KS et al (2015). [28]

Another recent study by Sunil B et al (2018) demonstrated that paracetamol is beneficial in ductal closure with low negative effects on Paracetamol. With intravenous paracetamol treatment, 27 out of 36 preterm newborns with hemodynamically significant PDA (hs-PDA) closed their PDAs (75%). On the other hand, Adriansyah R et al. examined the impact of intravenous paracetamol and discovered a 65.5% PDA closure rate after 14 days of testing.[29] In current study re-opening of duct was found in 6 (8%) in group I and 8 (10.7%) in group II. Adverse outcomes were renal failure, hyperbilirubinemia and gastrointestinal bleeding among both groups.[27-29]

A viable option to Ibuprofen for the medical closure of PDA is Paracetamol, which has less known side effects and theoretical benefits of improved PCM safety and tolerability.

CONCLUSION

We concluded in this study that the use of drug paracetamol is an effective for the closure of PDA in preterm neonates as compared to oral ibuprofen with less adverse outcomes and mortality rate.

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