Original Article

Comparison of Efficacy of Oral Ibuprofen and Oral Indomethacin in the Treatment of Patent Ductusarteriosus in Premature Neonates

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ABSTRACT

Objective: To compare the efficacy of oral ibuprofen and oral indomethacin in the treatment of patent ductusarteriosus in premature neonates.

Study Design: Comparative study

Place and Duration of Study: This study was conducted at the Neonatal care unit Bacha Khan Medical Complex Shah Mansoor Swabi from April 2018 to March 2020.

Materials and Methods: Through non-probability consecutive sampling technique, 120 premature neonates with patent ductusarteriosus (diagnosed as per criteria mentioned in operational definitions) were enrolled for this study and divided into two groups A & B, each with sample size 60. Group A was given oral ibuprofen (10 mg/kg stat followed by 2 doses of 5 mg/kg at 24 hours interval) and group B was given oral indomethacin (0.2mg /kg for 3 doses at 24 hours interval). Chi-square test was used to compare the efficacy between ibuprofen and indomethacin (in term of complete closure of PDA). The informed written consent was taken from parents of each patient. The permission of Ethical Committee was taken before collecting of data and gets publishing in Medical Journal. The finding of data was analyzed for results by SPSS version 20.

Results: In our study, there were 60 patients in each group. The mean age of patients in group A and group B were 8.45 days ±4.827 SD and 8.57 days ±4.996 SD respectively. The male to female ratio in group A &B was 1:1.14 and 1:1.40 respectively. The efficacy of PDA closure in group A was 78.3% (47/60) and in group B was 73.3% (44/60) with a p- value of 0.522 which was statistically not significant.

Conclusion: In our study, oral ibuprofen is as effective as oral indomethacin in the treatment of PDA in premature neonates and is thus an easily available and cost effective alternative to indomethacin in treatment of PDA in premature neonates.

Key Words: Patent ductusarteriosus (PDA), premature neonates, ibuprofen, indomethacin

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INTRODUCTION

Fetal circulation is dependent on patency of ductusarteriosus. DA connects pulmonary artery to aorta and shunts blood away from lungs into umbilical placental circulation where gas exchange takes place. At birth, closure of DA is an important part of postnatal circulation.[1] In term neonates, the ductusarteriosus usually closes functionally within first few days of life which is followed by anatomical closure with vascular remodeling. In preterm neonates, the closure of ductus is either delayed or does not occur at all. The persistence of PDA in preterm neonates increases with decreasing gestational age and birth weight.[2] The incidence of PDA is 70% in premature neonates of less than 29 weeks gestational age and weighing less than 1000 grams. Male to female ratio is 2:1.[3]

PDA is one of the most common clinical findings and most frequent source of complications in premature neonates especially in association with respiratory distress syndrome(RDS).[4] Depending on the size of shunt through PDA, volume overloading usually results in congestive cardiac failure and increased interstitial edema eventually leading to respiratory distress,

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respiratory failure, apnea and increased risk of Broncho-pulmonary dysplasia. Also the steal phenomenon with diastolic run-off into the lungs via PDA results in reduction in blood flow in splanchnic, renal and cerebral blood flow leading to necrotizing entero-colitis(NEC), bowl perforation, worsening of renal function and intracranial hemorrhage(ICH)in premature neonates.[5.]

The classical signs of PDA are a hyper dynamic circulation, bounding pulses and increased pulse pressure, hepatomegaly and a left infraclavicularsystolic murmur.[6]. The identification was established by echocardiographic visualization of a Patent Ductus Arteriosis with Doppler flow demonstrating left to right or both direction shunting. There are three treatment options for PDA closure which include conservative management, pharmacological therapy and surgical ligation. The effectiveness of conservative management is controversial and Sekar SC in 2008 revealed that conservative management is associated with increased failure rate especially in low birth weight neonates.[7] Also, Surgical ligation which involves thoracotomy is associated with significant complications such as pneumothorax, chylothorax, infection, laryngeal nerve palsy, respiratory compromise, alteration in blood pressure, retinopathy of prematurity and death.[8, 9.] Thus, pharmacotherapy is considered to be the therapy of choice for the treatment of hemodynamically significant PDA.[7]. initially intravenous indomethacin was a conventional treatment for hemodynamically significant PDA in premature neonates but its use was associated with various side effects. Patel et Al in 1995 proposed intravenous ibuprofen to be an effective alternative to indomethacin in closure of PDA in premature neonates.[10] Similarly, double blind randomized multicenter controlled trial by Von Overmiere et Al in 1997 and in 2000 revealed that I/V ibuprofen is as effective as IV indomethacin in treatment of PDA in premature neonates with less side effects as regards to oliguria and raised serum creatinine[11,12]. Due to costs involved and difficulty obtaining IV medications in developing countries, Heyman et Al in 2003 conducted a pilot study using oral ibuprofen which revealed that oral ibuprofen suspension can be used as an effective and safe alternative for treatment of PDA in premature neonates. [13.] Cherif et Al in 2008 conducted a study comparing the efficacy of oral versus IV ibuprofen in PDA closure in premature neonates and demonstrated a better closure rate with oral ibuprofen versus IV ibuprofen (84.3% vs 62.5%) with less adverse events. Also studies have shown that oral ibuprofen is an equally effective and safe alternative to indomethacin in treatment of PDA in premature neonates[4,14,15]. As oral ibuprofen is easily available and associated with less side effects, the rationale of my study is to compare the efficacy of oral ibuprofen with that of oral indomethacin in treatment of PDA in premature neonates in our setting.

MATERIALS AND METHODS

This study was conducted at neonatal care unit Bacha Khan Medical Complex Shah Mansoor Swabi from 1st April2018 to 31st March2020. Through non-probability consecutive sampling technique, 120 premature neonates with patent ductusarteriosus (diagnosed as per criteria mentioned in operational definitions) were enrolled for this study and divided into two groups A & B, each with sample size 60. Group A was given oral ibuprofen (10 mg/kg stat followed by 2 doses of 5 mg/kg at 24 hours interval) and group B was given oral indomethacin (0.2mg /kg for 3 doses at 24 hours interval). Chi-square test was used to compare the efficacy between ibuprofen and indomethacin (in term of complete closure of PDA). The informed written consent was taken from parents of each patient. The permission of Ethical Committee was taken before collecting of data and get publishing in Medical Journal. The data was analyzed for results by SPSS version 20.

RESULTS

There were 60 patients in each group. In Group A, there were 28(46.7%) males and 32(53.3%) females. In Group B, there were 25 (41.7%) males and 35(58.3%) females. P value equals 0.581 and it is considered to be statistically not significant. The male to female ratio in Group A and B was 1:1.14 and 1:1.40 respectively.

The ages of premature neonates in Group A and B respectively were;

From 1 to 5 days of age were 18(30.0%) and 16(26.7%), From 6 to 10 days were 23(38.3%) and 25(41.7%), From 11 to 15 days were 12(20.0%) and 11(18.3%) and from 16 to 20 days were 7(11.7%) and 8(13.3%).

The mean age of patients in Group A and Group B were 8.45 days ± 4.827 SD and 8.57 days ± 4.996 SD respectively with an overall mean age of 8.51 ± 4.892 SD. P value equals 0.897 which is considered to be statistically not significant. (Table No.1).

Table No 1: Age Distribution of PDA Patients in Group A And Group B

Age in days	Group A N(%)	Group B N(%)		
1-5 days	18(30.0%)	16(26.7%)		
6-10 days	23(38.3%)	25(41.7%)		
11-15 days	12(20.0%)	11(18.3%)		
16-20 days	7(11.7%)	8(13.3%)		
Mean age ± SD	8.45±4.827	8.57±4.996	Total 8.51 ± 4.892	P value 0.897
Total	60(100%)	60(100%)		

The efficacy of PDA closure in premature neonates in Group A and B was 78.3%(47/60) and 73.3% (44/60) respectively with a P value of 0.522 (Chi square) and it is considered to be statistically not significant. (Table No.2).

Table No 2: Efficacy of PDA Closure in Group A And Group B

Efficacy	GroupA	GroupB	Total	P value (chi square)
Yes	47(78.3%)	44(73.3%)	91(75.8%)	
No	13(21.7%)	16(26.7%)	29(24.2%)	
Total	60(100.0%)	60(100.0%)	120(100.0%)	**0.522**

The age wise distribution of efficacy in Group A & B was as follows:

from 1-5 days of age it was 88.8%(16/18) in Group A and 87.5%(14/16) in Group B, from 6-10 days 86.8%(20/23) in group A and 80.0%(20/25) in group B, from 11-15days 66.6%(8/12) in Group A and 54.5% (6/11) in Group B and from 16-20 days it was 42.8%(3/7) in group A and 50.0%(4/8) in group B.

The gender wise distribution of efficacy in Group A & B was as follows: in group A the rate of ductal closure was 82.1%(23/28) in males and 75.0%(24/32) in females and in group B it was 72.0%(18/25) in males and 74.1%(26/35) in females. (Tables No.3).

Table No.3: Gender Distribution Efficacy

Gender	Group A		Group B	
	Total patients	Efficacy	Total patients	Efficacy
Male	28	23(86.1%)	25	18(72.0%)
Female	32	24(75.0%)	35	26(74.1%)

DISCUSSION

In this study, we compared the efficacy of oral ibuprofen with that of oral indomethacin in term of complete closure of PDA in premature neonates. In our study, the efficacy of PDA closure in ibuprofen group was 78.3%(47/60) and in indomethacin group was 73.3%(44/60) with a p- value of 0.522. Our this result is supported by a study conducted by Pourarian SH et al[4]in which the rate of ductal closure was 80%(8/10) in ibuprofen group and 70%(7/10) in indomethacin group with a p- value >0.05. Similar results had been shown by other studies comparing oral ibuprofen and indomethacin. Fakhree SH et al in 2007 conducted a Randomized controlled trial in Iran using oral ibuprofen and indomethacin for the treatment of PDA in premature neonates and revealed that oral ibuprofen is as efficacious as oral indomethacin for treatment of PDA in premature neonates (100% vs 83.3% with a p-value > 0.05).[16.]Suppapannachat et al[17] compared 18 babies less than 34 weeks of gestational age with PDA and who were randomly assigned to treatment to either oral or IV indomethacin versus oral ibuprofen. They found comparable closure rates (78% in ibuprofen group and 89% in indomethacin group with a p-value > 0.05) in their small sample size with ibuprofen group having better urine output and concluded that oral ibuprofen therapy is as effective as indomethacin for the treatment of PDA in premature neonates with less renal side effects. Chotigeat et al [18] conducted a Randomized trial comparing efficacy of oral ibuprofen and indomethacin for treatment of PDA and concluded that ibuprofen has same efficiency as indomethacin (46.6% vs 66.6% RR 0.669; 95% CI. 0.328-1.364: p=0.462) in the treatment of symptomatic PDA in premature neonates with less chances of NEC and renal toxicity.

Neumann R et al[19] performed a systemic review and meta-analysis in 2012 and concluded that oral ibuprofen is almost equally effective to IV ibuprofen and IV indomethacin in the treatment of PDA in premature neonates. Lee SJ et al [14] compared the efficacy of oral ibuprofen and IV indomethacin and concluded that oral ibuprofen has advantages of simple administration and lower cost while being as effective as indomethacin (88.9% vs 87.5%). Similarly, Yang EM et al [20] conducted a randomized controlled trial in 2012 comparing the efficacy of oral ibuprofen and IV indomethacin for the treatment of PDA in extremely low birth weight(ELBW) neonates and concluded that in ELBW neonates, oral ibuprofen has same efficacy as IV indomethacin for treatment of PDA (81.8%vs 88.5%)with no difference between two drugs with respect to safety and thus oral ibuprofen can be used as an alternative agent for treatment of PDA in ELBW neonates. In 2014, Yadav S et al [21] compared the efficacy of oral ibuprofen and oral indomethacin for PDA closure in Indian preterm neonates and concluded that oral ibuprofen is as effective as oral indomethacin (60% vs 65.7%)with closure rates significantly higher at an early postnatal age. Almawazini AM et al [21] in 2015 also conducted a randomized controlled trial comparing the efficacy of oral ibuprofen versus IV indomethacin for treatment of PDA in preterm neonates and revealed that oral ibuprofen is equally effective to IV indomethacin for closure of PDA (91.3% vs 89.4%) and is associated with significantly less complications. Recent Cochrane review conducted in 2020 which comprises of 39 studies enrolling 2843 neonates concluded ibuprofen to be as effective as indomethacin in closing a PDA with reduced risk of NEC and transient renal insufficiency and thus appears to be the drug of choice. Oral administration of ibuprofen is equally effective to IV administration. [21]

In our study, efficacy of ductal closure in both groups decreased as the age of patients increased. This is supported by studies that showed a waning role of prostaglandins in maintaining ductal patency with increasing postnatal age[.21].

CONCLUSION

From the results of this study, it is concluded that oral ibuprofen is as effective as oral indomethacin in the

treatment of patent ductusarteriosus in premature neonates. As oral ibuprofen is cheap and easily available, it can be used as an effective alternative to indomethacin in premature neonates in our setting.

Author's Contribution:

Concept & Design of Study:	Bibi Asma
Drafting:	Mohammad Shafiq, Sara Gul
Data Analysis:	Faiza Akram, Sajjad ur Rehman, Asma Khan
Revisiting Critically:	Bibi Asma, Mohammad Shafiq
Final Approval of version:	Bibi Asma

Conflict of Interest: The study has no conflict of interest to declare by any author.

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