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Efficacy of Oral Paracetamol Over Oral Ibuprofen in Closure of Patent Ductus Arteriosus in Preterm Neonates: A Randomised Controlled Non Inferiority Study

[1]Pallavi Charanthimath, [2]Anita Daddi, [3]B.C. Yelamali, [4]M.S. Sheela and [5]Gajanan T. Magadum

[1-5]Department of Paediatrics, S Nijalingappa Medical College, Bagalkot, Karnataka, India

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Corresponding Author
M.S. Sheela,
Department of Paediatrics, S Nijalingappa Medical College, Bagalkot, Karnataka, India

Author Designation
[1,2,4]Assistant Professors
[3]Professor
[5]Post Graduate

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ABSTRACT

Ductus arteriosus (DA) is an essential vascular shunt during foetal life that connects the pulmonary artery with the aorta. During the embryo period, this shunt diverts blood from the pulmonary bed to the systemic circulation. In term neonates, in normal physiologic conditions, this arterial duct closes spontaneously up to by 72 hours. But in few cases, especially in preterm neonates this duct does not close after birth, which is called as patent ductus arteriosus (PDA). This PDA if left untreated leads to depression in respiratory capacity and shunt formation. Incidence of failure of the DA to close after birth is inversely proportional to gestational age (GA), with an incidence as high as 60% in 32 week preterm neonates. Patent ductus arteriosus (PDA) is a common cause of morbidity in premature neonates. The purpose of this study is to compare the efficacy of oral ibuprofen and oral paracetamol for closure of hsPDA, in premature neonates with gestational age (GA) <37 weeks. This study is a randomized clinical trial with 50 preterm neonates who were admitted in neonatal intensive care unit with hsPDA and GA <37 weeks. 25 neonates received oral ibuprofen and 25 neonates received oral paracetamol and compared with echocardiography finding of each groups for closure of PDA before and after treatment. Our results showed that, closure rate of PDA is 88% (i.e. n=22) and 88% (i.e. n=22) in the ibuprofen and paracetamols groups, respectively and statistically no significant difference was observed between the two groups (P=0.74). These findings suggest that there is no significant difference between the effectiveness of oral paracetamol and oral ibuprofen on closing of hsPDA, but less adverse effects with oral paracetamol making it reasonable choice for the treatment of hsPDA.

INTRODUCTION

Patent Ductus Arteriosus is a major morbidity seen in preterm neonates with incidence being inversely related to gestational age and birth weight. Studies report incidence of 15-40% in Very Low Birth Weight<1500 gram, whereas in preterm Extremely Low Birth Weight neonates <28 weeks,<1000 gram the incidence is as high as 50-65%[1,2]. The closure of ductus arteriosus (DA) following birth is an important component of transitional circulation, thereby directing the entire right ventricular output to the lungs to facilitate its oxygenation. Contrary to this the ductus arteriosus acts as conduit for diverting the partially oxygenated blood to support systemic circulation in foetus. The presence of PDA has significant effects on myocardial functions as well as systemic and pulmonary blood flow. Shunting from systemic to pulmonary circulation called ductal steal may lead to systemic hypoperfusion and pulmonary over perfusion. Hence hemodynamically significant PDA has negative effect on circulation of vital organs. Hemodynamically significant PDA is associated with a prolonged ventilation need and carries an increased risk of serious morbidities such as intraventricular haemorrhage, acute pulmonary haemorrhage, necrotising enterocolitis, chronic lung disease, broncho pulmonary dysplastic and increased mortality. Until recently, active PDA closure was considered beneficial[3-5]. Cyclooxygenase inhibitors, ibuprofen or indomethacin, are used as first line of treatment to promote ductal closure[6,7]. Surgical closure may be indicated if pharmacological therapy fails, or when contraindications to cyclooxygenase inhibitors are present[8,9]. The theoretical rationale for PDA treatment is unquestionable, but trials showing long-term benefits from PDA treatment are scarce[3]. Moreover, surgical closure has been associated with adverse outcome though it has been debated that these studies have had problems with confounding by indication[10]. On the other hand, spontaneous PDA closure has recently been shown to be high, even among the most immature infants. Early treatment of PDA might thus expose infants, in whom ductus ultimately would close spontaneously, to unnecessary treatment with potent and potentially toxic drugs. Ibuprofen and indomethacin are the current standard drugs for closure of a hemodynamically significant patent ductus arteriosus (PDA) apart from surgical ligation. These drugs have many adverse effects involving the gut, kidneys and the pulmonary vasculature. Previously in case of ibuprofen and indomethacin contraindication, surgical ligation was the only option. The role of paracetamol as an alternative treatment for closure of hsPDA has gained attention in recent years because of its superior safety profile in comparison to cyclooxygenase inhibitors. Several recent observational studies and randomised controlled trial (RCT) studies also show that paracetamol may be as effective as ibuprofen and indomethacin for closing PDA of preterm infants, but with fewer side effects. However evidence regarding the indications, dosage, effectiveness and safety including the long-term effects of paracetamol are still incomplete or lacking. In this study we attempted to study the efficacy of oral paracetamol over oral ibuprofen in closure of hemodynamically significant patent ductus arteriosus.

MATERIALS AND METHODS

Objectives: To study the efficacy of oral paracetamol for closure of hemodynamically significant patent ductus arteriosus, in comparison to oral ibuprofen in preterm neonates.

Source of Data: Preterm babies with clinical and echocardiographic features of hsPDA were recruited from the NICU unit Hanagal Shri Kumareshwar Hospital, Bagalkot.

Study Design: Randomized controlled non inferiority trial. Randomization was done into two groups with each group containing 25 babies, i.e. Group A and Group B. (Group A=Ibuprofen and Group B=Paracetamol).

Study Period: 1.6 years.

Place of Study: H. S. K. Hospital and Research Centre, SNMC Bagalkot.

Sample Size: Sample size estimation was done using Sample size 0.6.0 software for non inferiority trial. Sample size estimation was done using open epi software version 2.3.1. At 95% confidence level and 80% power of the study a (two-tailed)=0.250 and at 97.5% confidence level. ß=0.200 and 80% of power of the study. The standard normal deviate for a=Za=2.30 The standard normal deviate for ß=Zß=0.842 Non-inferiority margin of 0.2%. According to the study conducted by Kumar A, *et al,* Proportion of Study subjects with closure of PDA with Paracetamol group (Per protocol analysis)=95.4 %(p1). Proportion of Study subjects with closure of PDA with Ibuprofen group=94 %(p2). Sample size estimated is 22=25 in each group. i.e., 25 in Paracetamol group and 25 in Ibuprofen group.

Inclusion Criteria: Preterm neonates meeting criteria of hsPDA were included in the trial. Hemodynamically significant pda (hs PDA) is defined as either PDA with transductal diameter of >1.5 mm along with at least 2 of the predefined set of abnormal clinical signs or PDA

Table 1: Association of PDA Closure in Relation to Gestational Age

Outcome	GA IN WEEKS					
	Group-A(n=25)			Group-B(n=25)		
	< 32	32 – 35	> 35-36+6	< 32	32 - 35	> 35-36+6
Closed after 1st Course	4	11	0	0	9	4
Closed after 2nd Course	0	5	2	2	6	1
Failure	1	2	0	1	2	0
Total	5	18	2	3	17	5

Table 2: Association of PDA Closure in Relation to Birth Weight

Outcome	Birth Weight (In grams)					
	Group-A(n=25)			Group-B(n=25)		
	< 1000	1000 - 1500	> 1500	< 1000	1000 - 1500	> 1500
Closed after 1st Course	2	5	8	0	3	10
Closed after 2nd Course	0	2	5	1	2	6
Failure	0	1	2	0	1	2
Total	2	8	15	1	6	18

Table 3: Association of PDA in Relation to 2D-ECHO

2D ECHO	Group-A(n=25)		Group-B(n=25)		
	Before Treatment	After Treatment	Before Treatment	After Treatment	Total (n=50)
OPEN	25.00	3.00	25.00	3.00	50
CLOSED	0.00	22.00	0.00	22.00	44

Table 4: Association of PDA Closure in Relations to Complications

Outcome	ASSOCIATED COMPLICATIONS	
	Group-A(n=25) YES	Group-B(n=25) YES
Closed after 1st Course	1	1
Closed after 2nd Course	1	0
Failure	2	0
Total	4	1

Table 5: Comparison of Outcome with Group A and Group B

OUTCOME	Group-A(n=25)		Group-B(n=25)		Total(n=50)	
	Count	%	Count	%	Count	%
IMROVED AFTER 1ST COURSE	15	60	13	52	28	56
IMROVED AFTER 2ND COURSE	7	28	9	36	16	32
FAILURE	3	12	3	12	6	12
TOTAL	25	100	25	100	50	100

with transductal diameter of >1.5 mm along with the presence of 1 or more echocardiographic signs suggestive of hsPDA even in the absence of clinical signs.

Exclusion Criteria: Preterm with suspected/ diagnosed structural heart diseases, major congenital malformations, Preterm with contraindications for enthral feeding, Preterm with contraindications for administration of any of the study drugs(blood urea >60mg/dl, serum creatinine >1.6mg/dl, platelet count <60000/ul, clinical bleeding from any site, necrotizing enterocolitis, intraventricular haemorrhage.) And neonates whose parents refused consent. Ethical clearance was obtained from the Institutional Ethics Committee on Human subjects research. Written informed consent (in English and local language) was taken from all parents before enrolment in the study. Study design and administration of study drugs. Study subjects were randomly assigned to receive either oral paracetamol suspension (experimental arm) or oral ibuprofen suspension (active control arm). Paracetamol oral suspension was administered through an orogastric tube at 15mg/kg per dose in 6 hourly intervals for 3 consecutive days. Ibuprofen oral suspension (ibugesic) was administered at 10mg/kg/dose, followed by 5mg/kg/dose at 24 and 48 hours after the first dose. Transthorasic echocardiography was done 24 hrs after the completion of course. PDA closure was confirmed when there is no demonstrable open ductus or no flow on colour Doppler. Those babies in whom hsPDA remained open or reopened, were administered a second course(same dose) of the study drug. If the ductus remains open even after second course, is considered as failed and those babies were referred for surgery. Following radiological parameters were assessed during the study.

Radiological Parameters: ECHO.

- Transductal diameter
- **Left Atrium:** Aorta root diameter ratio.

- Ductal velocity.
- Mitral inflow velocity E/A ratio.
- Absent or reversed diastolic flow in descending thoracic aorta.

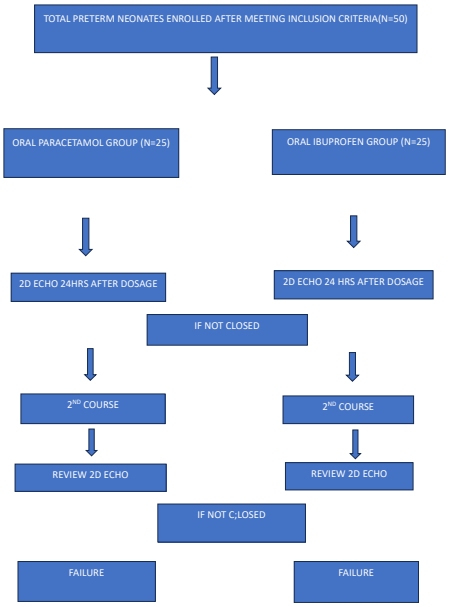

Fig 1: Total Preterm Neonates Enrolled after Meeting Inclusion Criteria

RESULTS AND DISCUSSIONS

Among the total study subjects, majority of the study subjects belonged to 32-35 weeks gestational age class interval (n=35, 70%) i.e. 18 and 17 in Group A and Group B respectively. In PDA closed group, majority of the study subjects belonged to 32-35 weeks gestational age class interval (n=31, 62%) ,i.e. 16 in Group A (11 After 1st course and 5 after 2nd course) and 15 in Group B (9 After 1st course and 6 After 2nd course). Among PDA closed study subjects, 22(88%) got closed in Group A (15 after 1st course and 7 after 2nd course) and 22(88%) got closed in Group B (13 after 1st course and 9 after 2nd course). Among PDA not closed Group, 3(12%) did not close in Group A and Group B respectively i.e. Failure. These failure cases were referred for surgery. In our study 50 infants with gestational age <36+6 weeks treated with15mg/kg every 6hr for 3days of paracetamol and found that ductus was closed in 88% of paracetamol group and similarly in ibuprofen group (i.e. 88%)and the incidence of hyperbilirubinemia or gastrointestinal bleeding was significantly lower in the paracetamol group. In paracetamol group, PDA closure was evident in 22(88%) babies with no significant side effects. In our study, there is no much difference in the closure rate of PDA ,but there is significantly lesser side effects with Oral paracetamol group compared to oral ibuprofen group. Out of 25 babies in each group, In 15(60%) babies PDA got closed after 1st course of treatment in Group A and 13(52%) in Group B. Hence our study shows that paracetamol is as effective as ibuprofen in closure of hsPDA with lesser side effects.

CONCLUSION

In closure of hsPDA paracetamol is an equally effective, promising new alternative to ibuprofen. It is the treatment of choice in several scenarios where ibuprofen is contraindicated. However more studies are necessary to know about optimal dose, route of administration and long term adverse effect on growing brain. The lesser no of samples in our study is the main limitation and therefore multicentre studies are needed to collect adequate numbers of cases to resolve it. Oral paracetamol can be used as first line pharmacological management for hsPDA due to lesser side effects, easy availability and equally effective.

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