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Research Article

USE OF INTRARECTAL PARACETAMOL IN PRETERM NEONATES WITH PDA CLOSURE

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Abstract

Patent ductus arteriosus (PDA), in which there is a persistent communication between the descending thoracic aorta and the pulmonary artery that results from failure of normal physiologic closure of the fetal ductus, is one of the more common congenital heart defects in Preterm neonates. The closure of PDA can be done with either Indomethacin/Ibuprofen which are cyclooxygenase 1, 2 inhibitor; however these drugs are associated with side effects. We report an interesting findings of ductal closure in 11 preterm neonates presenting with significant large PDA who had contraindication with Indomethacin/Ibuprofen/oral use.These Preterm neonates were treated with intrarectal Paracetamol in the dose of 15 mg/kg/dose 8 hourly for a period of 48 hours. Rectal administration is preferred during this study because of feed intolerance/NEC/ restricted oral intake/nausea/vomiting/gastric dysfunction. The PDA closure was achieved within 72 hours in 90.9%[10 babies] and there was no complications.

Keywords: Ductus, Ibuprofen, Indomethacin, Paracetamol,Preterm

INTRODUCTION

A persistently Patent ductus arteriosus (PDA) has significant clinical consequences in Preterm neonates during the recovery period from respiratory distress syndrome [1].Ductal patency is regulated by the circulating prostaglandins (PGs) produced by an enzyme system, namely prostaglandin-H2 synthetase (PGHS), which is composed of two active sites: cyclo-oxygenase (COX) and peroxidase [2,3].Indomethacin/Ibuprofen are COX-inhibitor drugs commonly used for the treatment of hemodynamically significant (hs)-PDA. Despite the about 70% success rate, COX-inhibitors are frequently contraindicated in early life and their use has been associated with serious adverse events, such as gastrointestinal perforation, renal failure and bleeding [4-11]. Paracetamol, an inhibitor of the peroxidase component of PGHS, is commonly used in pediatric age, and has been recently proposed for the treatment of PDA [12-22]. We aimed to evaluate the efficacy of intrarectal Paracetamol in the early treatment of PDA in Preterm neonates presenting contraindication to COX-inhibitors/Oral use.

MATERIALS & METHODS

Inclusion criteria;

1.Gestational age less than 34 weeks
2.Significant PDA

Exclusion criteria;

1.Gestational age 34 weeks or more
2.Associated other congenital cardiac anomalies

It was observational study for 24 months from January 2013 to December 2014.

An ethical committee consent was taken to use intrarectal Paracetamol for Patent ductus closure in Preterm neonates with significant PDA who had contraindication for Ibuprofen/Indomethacin use/oral use.In addition Parental consent was taken before the study.Rectal administration is preferred during this study because of restricted oral intake,feed intolerance,NEC and gastric dysfunction.Out of 273 NICU admissions,there were 33 Preterm neonates who had PDA, out of these 23 were with significant PDA which required treatment. All these Preterm neonates were diagnosed to have hemodynamically significant PDA[size more than 3 mm,left atrium to aortic ratio is 1.8 / more,haemodynamically unstable] at 4-7 days of life by Paediatric Cardiologist.Oral Ibuprofen was given to 12 Preterm neonates and 11 were given intrarectal Paracetamol as Ibuprofen/Indomethacin/oral use was contraindicated. Each of these 11 Preterm neonates were given intrarectal Paracetamol in the dosage of 15 mg/kg/dose 8 hourly for 48 hours. These Preterm neonates were monitored for temperature variation before and 30 min after giving intrarectal Paracetamol administration. The ductal closure was confirmed with repeat echocardiography after 72 hours of administration.

RESULTS

Gestational age in weeks	Birth weight in grams	Echocardiographic findings	Number of dosage of intrarectal PCT
28	900	PDA L-R Shunt Size 5 mm MPAP -42 mm of hg PSPAP-50 mm of hg Left atrium to aortic root ratio 1.9	6
28	950	PDA L-R Shunt Size 4 mm MPAP -40 mm of hg PSPAP-48 mm of hg Left atrium to aortic root ratio 1.8	6
30	1020	PDA L-R Shunt Size 6 mm MPAP -50 mm of hg PSPAP-60 mm of hg Left atrium to aortic root ratio 2	6
31	1150	PDA L-R Shunt Size 5 mm MPAP -42 mm of hg PSPAP-50 mm of hg Left atrium to aortic root ratio 1.9	6

31	1200	PDA L-R Shunt Size 4.5 mm MPAP -48 mm of hg PSPAP-58 mm of hg Left atrium to aortic root ratio 2.2	6
32	1200	PDA L-R Shunt Size 6 mm MPAP -50 mm of hg PSPAP-60 mm of hg Left atrium to aortic root ratio 2	6
32	1330	PDA L-R Shunt Size 5 mm MPAP -42 mm of hg PSPAP-50 mm of hg Left atrium to aortic root ratio 1.9	6
32	1300	PDA L-R Shunt Size 4 mm MPAP -40 mm of hg PSPAP-48 mm of hg Left atrium to aortic root ratio 1.8	6
32	1350	PDA L-R Shunt Size 6.5 mm MPAP -50mm of hg PSPAP-60 mm of hg Left atrium to aortic root ratio 1.9	6
33		PDA L-R Shunt Size 4 mm MPAP -48 mm of hg PSPAP-56 mm of hg Left atrium to aortic root ratio 1.8	6
33	1410	PDA L-R Shunt Size 4.5 mm MPAP -40 mm of hg PSPAP-48 mm of hg Left atrium to aortic root ratio 1.8	6

Out of 23 Preterm babies with significant PDA,12 Preterm babies were given oral Ibuprofen,the ductal closure was achieved in 83.3%[10 babies] with feed intolerance in 16.6%[2 babies] where as 11 Preterm babies who were given intrarectal Paracetamol ductal closure was achieved in 90.9%[10 babies] by 72 hours of administration confirmed by echocardiography without any complications.

DISCUSSION

Approximately, 70-80% of Preterm neonates require pharmacologic and/or surgical intervention to close a hemodynamically significant Patent ductus arteriosus (PDA). Indomethacin has been the pharmacologic treatment of choice and has also been used prophylactically in very Premature neonates to prevent PDA.[23,24] The drug, however, is associated with gastrointestinal and renal adverse effects. In July 2006, intravenous Ibuprofen became available in the United States of America for treatment of hemodynamically significant PDA. The mechanism of action for both Indomethacin and Ibuprofen is through inhibition of prostaglandin synthesis, resulting in ductal constriction. Both drugs appear to be equally efficacious in closing echocardiographically confirmed PDA. Ibuprofen has demonstrated significantly less effects on cerebral, renal, and mesenteric blood flow in Premature neonates when compared with Indomethacin.[25,26] A transient but significant increase in serum creatinine concentration, decrease in urine output, and increase in frequency of oliguria,bleeding tendencies,bronchospasm were observed with Indomethacin when compared with Ibuprofen. However, the rate of reopening of the ductus after pharmacologic closure and the need for rescue therapy were not different between the two drugs. In addition, no differences were noted in other outcomes such as frequency of intraventricular hemorrhage, necrotizing enterocolitis, or chronic lung disease, as well as in duration of mechanical ventilation and length of hospital stay.[25,26]

The Paracetamol also inhibits prostaglandin synthetase activity. Although its precise mechanism of action remains controversial, Paracetamol seems to act at the peroxidase segment of the enzyme. Peroxidase is activated at 10-fold-lower peroxide concentrations than is cyclooxygenase.[27,28] Therefore, Paracetamol-mediated inhibition is facilitated at reduced local peroxide concentrations (hypoxia). Theoretically, these differences would permit peroxidase inhibition to be optimally effective under conditions in which cyclooxygenase inhibition is less active or hypothetically, render it ideally suited for treatment in the PDA environment. The exact mechanism use of Paracetamol in ductal closure has not been studied on large scale; however with this study it is evident that intrarectal Paracetamol is equally effective in ductal closure with no side effects which was there with Ibuprofen/Indomethacin. Although interesting, the results of our study suffer from some limitations, on a limited number of Preterm neonates.However, a large randomized study is needed to validate this interesting observation.

CONCLUSION

Our study demonstrates the efficacy of intrarectal Paracetamol in closure of PDA in Preterm neonates with contraindication to Indomethacin/Brufen/oral use with efficacy of 90.9% with no complications.

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