Original Research Paper

Volume - 11 | Issue - 01 | January - 2021 | PRINT ISSN No. 2249 - 555X | DOI : 10.36106/ijar

Paediatrics

PARACETAMOL FOR CLOSURE OF PATENT DUCTUS ARTERIOSUS IN PRETERM NEONATES ADMITTED TO A TERTIARY CARE CENTRE

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ABSTRACT

Background: Ductus arteriosus is a vascular connection between the pulmonary artery and descending aorta. The incidence is inversely related to birth weight and gestational age (GA). In preterm infants it varies between 40% and 60% on the third day of life. At present, the choice of treatment of clinically significant PDA is with either ibuprofen or indomethacin, but they carry many contraindications and potential side effects. Hence it is important to consider that paracetamol may be used as an alternative to other non steroidal anti-inflammatory drugs and is effective in ductal closure with minimal side effects.

Methods: 32preterm infants with hemodynamically significant PDA(hs-PDA) were treated with intravenous paracetamol and subsequent closure was evaluated clinically and by follow-up 2D-Echo.

Results: PDA closure following intravenous paracetamol was evident in 26 babies (68%). No significant side effects noted with paracetamol therapy were noted.

Conclusions: This study shows that paracetamol could offer favourable safety profile in comparison to current treatment options. Therefore, paracetamol may be accepted as a first-line drug treatment for PDA in preterm infants.

KEYWORDS : Paracetamol, Patent ductus arteriosus, Preterm

INTRODUCTION

The presence of patent ductus arteriosus was originally recognized by Galen in the 2nd century AD. The first surgical ligation of PDA was performed in 1938 by Robert E. Gross of Bostons Childrens' hospital.[1]

Ductus arteriosus (DA) is the shunt that makes communication between pulmonary artery to aorta and it is one of the basic shunts necessary in the prenatal life to maintain fetal circulation.[2]

Ductus arteriosus is a vascular connection between the pulmonary artery and descending aorta, through which the deoxygenated blood returning to the right heart is diverted to placenta for reoxygenation during fetal life.

The incidence is inversely related to birth weight and gestational age [3]. Incidence in VLBW 15-40% whereas in prematurity, the incidence is as high as 50-65%.

Normally patency of the fetal ductus arteriosus is mainly controlled by relatively low fetal oxygen tension and PGE2 and PGI2.[8,9] Locally produced and circulating PGE2 and PGI2 cause vasodilation of the fetal ductus arteriosus via interaction with ductal receptors.[10]

Circulating PGE2 and PGI2 levels are high in the fetus because of synthesis by the placenta and decreased metabolism in the fetal lungs.

After birth, there is abrupt increase in oxygen tension which inhibits ductal smooth muscle voltage-dependent potassium channels, and results in an influx of calcium and ductal constriction.[11] PGE2 and PGI2 levels decreases as metabolism in the functioning lungs begins and elimination of the placental source. Ductal medial smooth muscle fibres contract, which results in thickening of wall with obliteration of lumen, and shortening of the ductus arteriosus.

Functional complete closure usually occurs within 48 hours of birth in term neonates. Over next 2 to 3 weeks, infolding of the endothelium along with disruption of intima, proliferation result in fibrosis and a permanent closure.[12]

Even though small PDAs may be asymptomatic, larger PDAs are clinically significant. PDAs that are large, symptomatic, or persistent despite medical therapy require surgical intervention. [13] Failure to closure of ductus in the preterm infants for long period of time leads to severe respiratory distress, requiring prolonged ventilatory support, and increases chances of pulmonary hemorrhage, bronchopulmonary dysplasia, necrotizing enterocolitis, renal functional impairment, intraventricular hemorrhage, periventricular leukomalacia, and death.[14]

A hemodynamically significant PDA can be defined as:

Clinical

- Hyperdynamic precordium
- Systolic murmur
- Bounding peripheral pulses
- Wide pulse pressure
- 2D ECHO
- DA diameter ≥ 1.5mm
- LA/Ao ≥1.5
- Diastolic turbulence on doppler in pulmonary artery

Pharmacological PDA treatment has, for the past 4 decades,largely consisted of non-selective cyclooxygenase (COX) inhibitors (e.g., ibuprofen and indomethacin). Although early treatment has high efficacy for ductal closure (60–80%),failure to improve many clinical outcomes, in addition to treatment-associated complications (e.g., acute renal injury, oliguria, and gastrointestinal hemorrhage), has prompted thesearch for an alternative agent with higher efficacy and an improved adverse effect profile.

Recent studies have shown that paracetamol, a common antipyretic and analgesic drug can be used as an alternative to treat PDA in preterm with good efficacy and less side effects.[25]

The prostaglandin-H2 synthetase (PGHS) enzyme system has two active sites: the cyclo-oxygenase (COX) and peroxidase (POX) sites. PGHS produces circulating prostaglandins (PG) that help to regulate the ductal patency.[26,27] The COX site converts arachidonic acid to PGG2 by oxidation, subsequently converted to PGH2 by the POX site. After formation of PGH2, it is subsequently converted to PGF2α, PGE2, PGI2 or TXA2. Non- selective COX inhibitors like NSAIDS inhibit COX site while paracetamol inhibit the POX site (Figure 1).[28]

Paracetamol hereby acts as a reducing co-substrate so that less PGG2 can be converted to PGH2. Hence it is important to consider that paracetamol may be used as an alternative to other NSAIDS and is effective in ductal closure with minimal side effects.

MATERIAL & METHODS

This study was conducted in Neonatal Intensive Care Unit of Paediatrics Department at Jawahar Lal Nehru Medical College Hospital Bhagalpur, a tertiary care teaching hospital in Eastern Bihar. Ethical approval for the study was obtained from the Institutional Ethical Committee. It was Hospital based prospective study and 32 preterm neonates were included in the study.

Inclusion Criteria

- Gesational age of >26 weeks and < 37 weeks
- Haemodynamically significant PDA size >2mm (diagnosed by 2D-Echo within first 72 hours of life)

- Those in whom indomethacin and ibuprofen is contraindicated (proven sepsis, active bleeding - intracranial or GI Bleed, suspected NEC, thrombocytopenia, significant impairment of renal function (i.e. urine output <1ml/kg/hr).

Exclusion criteria

- Major congenital malformations,
- Echocardiographic evidence of pulmonary hypertension,
- Participation in another trial involving any investigational drug,
- Previous treatment with paracetamol, ibuprofen or any COX inhibitor for any purpose.

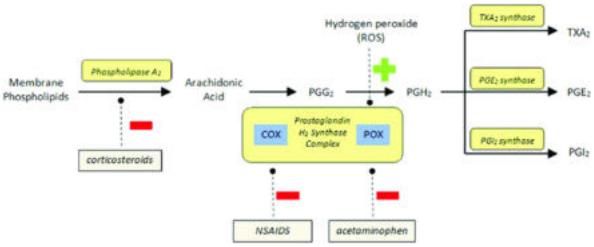


Figure 1: The prostaglandin-H2 synthetase (PGHS) enzyme system.

Written informed consent was taken from parents/guardians of all eligible subjects in their preferred language. Complete maternal history was taken, Complete history and physical examination was carried out in all neonates included in the study. Demographic and clinical variables were recorded. It included birth weight, sex, gestational age, mode of delivery

The babies diagnosed by 2D-Echo within first 72 hours of life with haemodynamically significant PDA (hsPDA) size >2mm received intravenous paracetamol 15mg/kg/dose 6th hourly for 3 days and subsequent closure was evaluated clinically and follow-up 2D-Echo.

RESULTS

A total of 32 preterm neonates who met the inclusion criteria were studied from October 2018 to February 2020.

Average gestational age of the study subjects were 30±2 weeks, birth weight of 1200±250 g and Apgar score 7±1.

Out of 32 preterm neonates, 14 (43.75%) were male and 18(56.25%) were females. 12 (37.5%) of 32 babies were delivered through caesarean section and remaining 20(62.5%) through vaginal delivery.

It was noted on 2D ECHO that these 32 babies had a ductal diameter >2mm.

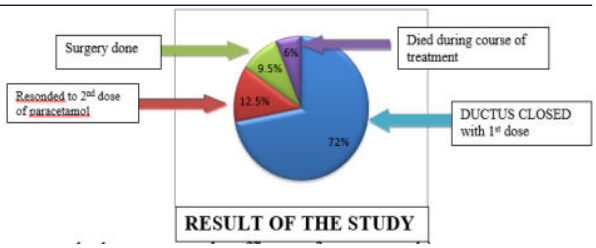
32 babies who received IV paracetamol, PDA closure was evident in 23babies (72%) by 2D ECHO. There were no significant side effects noted with paracetamol therapy.

After the 1st course of treatment with paracetamol, 9(28%) infants in whom ductus did not close, follow up 2D ECHO was done.

Demographic Features Of The Newborn	
VARIABLE	MEAN AND NUMBER
Birth Weight (gm)	1200±250
Gestational Week	30±2
Type of Delivery Vaginal Cesaean	 20 (62.5%) 12(37.5%)
Sex Male Female	 14(43.75%) 18(56.25%)

In the remaining 9 neonates, 2 babies succumbed to their grave condition i.e. and the rest 7 received 2nd dose of Paracetamol and successful closure was noted in 4 of them. Out of these, 3 neonates didn't respond to 2nd dose of paracetamol and required surgical intervention.

Present study demonstrates the efficacy of paracetamol in preterm neonates with hsPDA with contraindication to COX inhibitors. Hammerman et al reported the first case series of preterm infants and observed that oral paracetamol for a period of 3 days at a dose of 60 mg/kg/qid was effective in closing PDA.[23]



Oncel et al reported the results of ramdomised contolled trial in preterm infants treated with oral paracetamol in whom closue of PDA was acheieved with no side effects.[24]

According to Terrin et al a case series of neonates with hs-PDA treated with paracetamol because of contraindication to ibuprofen or indomethacin, ductal closure was noted in 70% of neonates with no adverse reactions likewise in our study ductal closure was noted in 75% neonates with IV paracetamol. The mechanism by which paracetamol can close ibuprofen refractory PDA might lie in the different site of action on prostaglandin synthetase of the two drugs, that hypothetically might have also a synergistic effect.[25]

Singh Y stated that paracetamol could be used to treat PDA, when established first line therapy (cyclo-oxygenase inhibitors) are either contra-indicated or have been ineffective.[26]

These data on the effectiveness of paracetamol for the treatment of PDA are very promising, as they suggest that if paracetamol will be confirmed to be effective in future randomized controlled trials, particularly as intravenous therapy, it may become the treatment of choice for the management of PDA.

CONCLUSION

The management of PDA should be individualized, according to clinical and echocardiographic finding of hemodynamic significance of PDA. As the available data do not support prophylactic or presymptomatic approach, expectant symptomatic treatment for hs-PDA seems to be the most reasonable approach.

Our data on the effectiveness of paracetamol in the treatment of PDA merits for conduction of further well designed randomized control trials, to confirm the usefulness of paracetamol as first choice agent in management of PDA due its lesser side effect profile. It may also be considered as an alternative to surgical ligation in whom ibuprofen is either contraindicated or resistant. Large, randomized, prospective studies to determine the optimal treatment strategy, regarding the effectiveness and safety of paracetamol to close a PDA is needed before recommendations for practice can be stated.

Ethical approval: The study was approved by the Institutional Ethics Committee

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