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Original Research Article

IV 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: Thirty six preterm 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 27 babies (75%). There were no significant side effects noted with paracetamol therapy.
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, Preterm infants, Patent ductus arteriosus

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 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 ductus arteriosus is a vital structure in fetus where the systemic and pulmonary circulations function in parallel so that cardiovascular function is totally dependent on the presence of shunts, such as ductus arteriosus and foramen ovale, between the two circulations.[2] The incidence is inversely related to birth weight and gestational age (GA).[3] In preterm infants it varies between 40% and 60% on the third day of life.[4-7]

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. Failure of closure of ductus arteriosus within 72 hours after birth results in significant morbidity and mortality that may approach 30%.[13]

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

At present, the choice of treatment of clinically significant PDA is with medication, either ibuprofen or indomethacin. The ductal closure rates of both the drugs are similar ranging from 70-80%.[14-16] Moreover, the complication is high and carries significant contraindications.[17-22] When drug fails or contraindicated, next option is surgery. But surgery carries significant mortality and morbidity.[23,24]

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. On a contrary, paracetamol related POX inhibition is counteracted by PGG2 itself or lipid hydroperoxides. 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.

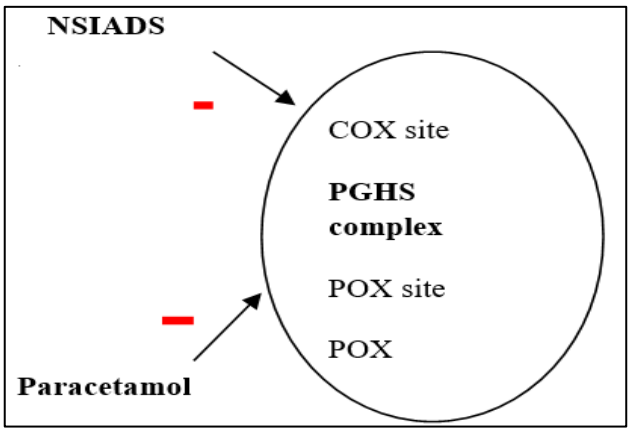

Figure 1: The prostaglandin-H2 synthetase (PGHS) enzyme system.

METHODS

It was a Prospective observational study. 36 Preterm Neonates admitted to Kempegowda Institute of Medical Sciences, NICU LEVEL-III from December 2015 to October 2016, were included in the study.

Inclusion criteria

- Gestational 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.

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.

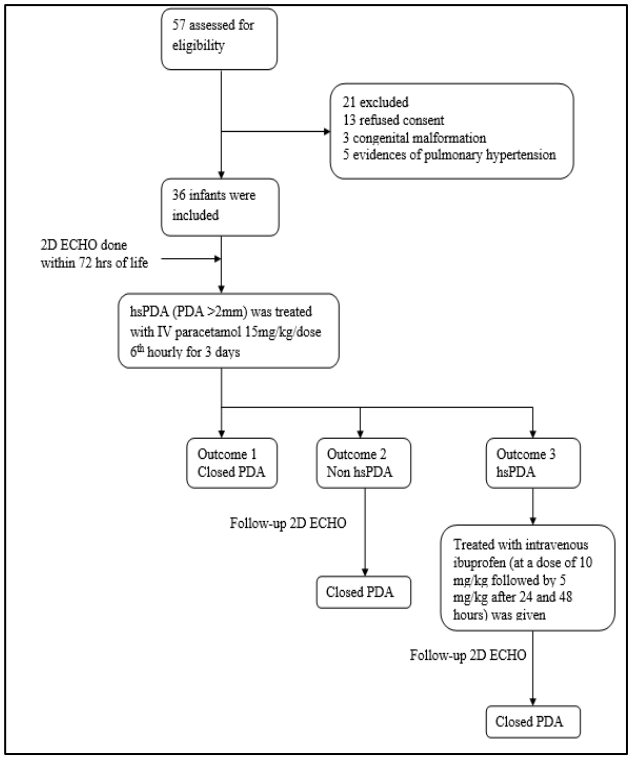

Figure 2: Study procedure flowchart.

RESULTS

A total of 36 preterm neonates who met the inclusion criteria were studied from December 2015 to October 2016. Average gestational age of the study subjects were 29±2 weeks, birth weight of 1203±170 g and Apgar score 6±1.

Out of 36 preterm neonates, 21 (58.3%) were male and 15 (41.7%) were females. 25 (69.4%) of 36 babies were delivered through caesarean section and remaining 11(30.6%) through vaginal delivery.

It was noted on 2D ECHO that these 36 babies had a ductal diameter >2mm.

Thirty six babies who received IV paracetamol, PDA closure was evident in 27 babies (75%) by 2D ECHO. There were no significant side effects noted with paracetamol therapy.

After the 1st course of treatment with paracetamol, 9 (25%) infants in whom ductus did not close, follow up 2D ECHO was done. One infant on follow up had non-hsPDA.

In the remaining 8 neonates, 3 babies succumbed to their grave condition i. e. intraventricular hemorrhage grade III and the rest 5 received intravenous ibuprofen (at a dose of 10 mg/kg followed by 5 mg/kg after 24 and 48 hours) considering that previous contraindications were no longer present and successful closure was noted. None of the neonates required surgical intervention.

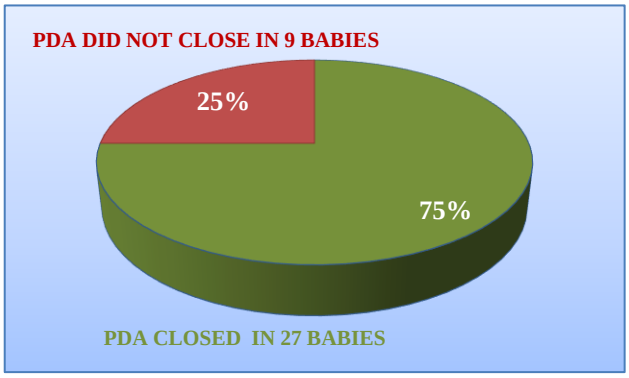

Figure 3: The result of PDA closure with IV paracetamol.

DISCUSSION

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.[25] 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.[29]

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.[30] 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.[31]

Sinha et al contrary to the prescribed ibuprofen, which had left many side effects, after administration of oral acetaminophen, no side effects were observed.[32]

Singh Y stated that paracetamol could be used treat PDA, when established first line therapy (cyclo-oxygenase inhibitors) are either contra-indicated or have been ineffective.[33]

Dang et al studied 160 infants with gestational age ≤34 weeks treated with 15 mg/kg every 6 h for 3 days of paracetamol or ibuprofen at standard dose.[34] They found that the ductus was closed in 81.2% of infants in the paracetamol group compared with 78.8% of infants in the ibuprofen group (p = 0.7), and that the incidence of hyperbilirubinemia or gastrointestinal bleeding was significantly lower in the paracetamol group.

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.

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

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