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**Original Research**

# Efficacy of Indomethacin in Pharmacological Closure of PDA in Preterm Neonates: A Prospective Study from Tertiary Care Centre in Rural India

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## ABSTRACT

**Background:** Patent ductusarteriosus (PDA) is a fetal shunt necessary for intrauterine survival of the baby, however its closure at birth occurs as pulmonary vascular resistance drops and lungs get expanded for participating in ventilation. However, PDA remains patent in a large proportion of preterm babies and by day -7, 87% of babies <24 wk gestation have a PDA which hinders in ventilation and causes ductal steal to vital organs. Hence, we aimed to study pharmacological closure of ductus in preterm babies. **Aims and Objectives:** 1) To study the efficacy of COX inhibitor, Indomethacin in ductal closure in preterm babies <34 wk gestation. 2) To compare the symptomatology of PDA in different groups of preterm babies <34 wk GA. **Methods:** A Hospital-based prospective study was conducted in tertiary care NICU.A total of 104 consecutive, eligible preterm babies <34 wk with echocardiographically documented PDA. Indomethacin (COX inhibitor) was administered orally in a dose of 0.2 mg/kg 12 h for 3 doses and the babies underwent Echo study in first 48 h, after2 days, 7days, and weekly thereafter till PDA closure. A second cycle of indomethacin was repeated if PDA did not respond to the initial treatment. **Results:** 75/104 (72%) PDAs closed with indomethacin while 13(12.5%) did not respond, and 16(15.38%) showed a reduction in the calibre of PDA. 26–30 wk group showed a brisk response to ductal closure with indomethacin within 108.1±12.44 h, and a mean no. of cycles of indomethacin of 0.98±5.75. **Conclusion:** With indomethacin we achieved 72% (75/104) closure rates. The best response to indomethacin was noted in 30–32 wk GA group, while maximum nonresponders were in 32–34 wk; suggesting as gestation increases, response to PG inhibitors decreases.

**KEYWORDS:** Patent ductusarteriosus, Cyclo-oxygenase, Indomethacin, Preterm Neonates, PG inhibitors, Ductus arteriosus, Ductal flow

## BACKGROUND

In fetal circulation, patent ductus arteriosus (PDA) is an important shunt to divert the RV blood to the descending aorta while the PVR is high, however soon after birth as PVR drops and SVR rises with the clamping of umbilical cord, ductal flow reverses, pulmonary alveoli open up and eventually the PDA closes functionally by 72 h of life in a term neonate. At birth, functional closure of this channel redirects blood flow to the pulmonary vascular bed and allows the lungs to start effective respiratory gas exchange. Closure involves interaction of oxygen, prostaglandins, nitric oxide and the unique musculature of the ductus arteriosus. In healthy term babies, ducts are functionally closed in 20% on day 1, 82% by day 2, 96% by day 3, and 100% by day 4 [1]. In preterm infants, however, closure is delayed, remaining open

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at 4 days of age in approximately 10% of infants born at 30 through 37 weeks' gestation, 80% of those born at 25 through 28 weeks' gestation, and 90% of those born at 24 weeks' gestation [2,3]. By day 7 after birth, those rates decline to approximately 2%, 65%, and 87%, respectively. The ductus is likely to close without treatment in infants born at >28 weeks' gestation (73%) [4] in those with birth weight >1000 g (94%) [5], and in infants born at 26 through 29 weeks' gestation who do not have respiratory distress syndrome (93%) [6]. Thus, the ductal patency in premature babies can hinder in oxygenation causing a ductal steal depriving vital organs of blood supply: viz., brain, kidney and intestine, hence the interest in pharmacological closure of ductus in preterm babies.

### Objectives

1. To study the efficacy of COX inhibitor: Indomethacin inductal closure in preterm babies <34 wk gestation.
2. To compare the symptomatology of PDA in different groups of preterm babies < 34 wk GA.

## MATERIAL AND METHODS

**Study design:** Hospital based prospective study.

**Sampling method:** 104 consecutive preterm babies<34 wk with echocardiographically documented PDA were enrolled in the study.

**Study duration:** Details recorded in a predesigned study format sequentially between 1st August 2012 and 31st July 2013.

**Study location**: The present was conducted in tertiary care NICU in Pravara Rural Hospital, Loni.

**Inclusion criteria:** Babies <34 wk GA with PDA documented on echo study.

**Exclusion criteria:** Late preterm and full term neonates, associated complex congenital heart disease where PDA was the sole source of pulmonary or systemic circulation, contra-indications for the use of indomethacin, viz., deranged renal profile, oliguria (<0.5 ml/kg/h) for 6 h, IVH, thrombocytopenia : platelet count <50,000/cmm, NEC defined by modified bells staging, intestinal perforation.

The babies were divided in three groups, viz., 26–30 wk, 30–32 wk, and 32–34 wk GA for the ease of comparison between these groups.

**Drug administration:** Indomethacin (COX inhibitor) was administered orally in a dose of 0.2 mg/kg 12 h for 3 doses and the babies underwent echo study in first 48 h, after 2 days, 7days and weekly thereafter till PDA closure. A second cycle of indomethacin was repeated if PDA did not respond to the initial treatment.

## METHODOLOGY

2 Dechocardiography/colourDoppler was performed on a Siemens echocardiography machine with a paediatric 5S probe with adjustable frequency for tinier babies. Echo was performed within the first 48 h of life to document PDA. A hemodynamically significant PDA (Figure 1) was defined as ductal size >1.5 mm at the ampulla, LA: aorta ratio of 1.5:1, evidence of left heart volume overload and diastolic run off in the descending thoracic aorta. 2D echo/colour Doppler was repeated after 2 days and 7 days and thereafter weekly if PDA persisted. X-Ray chest documented evidence of RDS and the effects of PDA on pulmonary

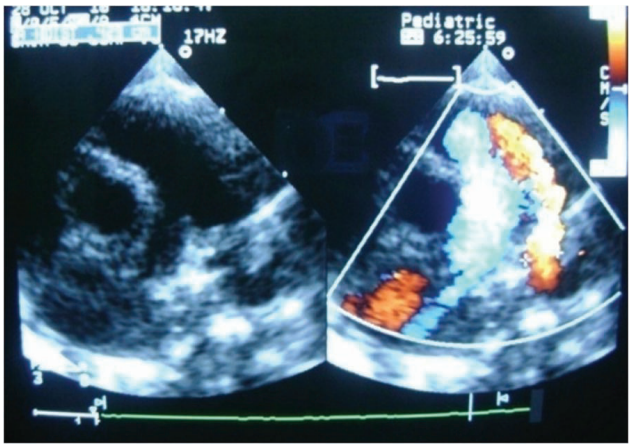


**Figure 1: PDA as seen in 2D echo/colour Doppler**

circulation. Indomethacin was given orally/Infant feeding tube mixed with expressed breast milk in a dose of 0.2 mg/kg every 12 h for three doses. A second cycle was repeated if PDA did not respond to the initial treatment.

### Statistical Analysis

Statistical analysis was done by applying descriptive statistics as mean, SD, proportions, etc. Comparisons made by applying ANOVA test and Tukey–Kramer multiple comparison test, Chi-Square test and *Z* test of difference between two proportions at 5% (*p*,0.05) and 1% (*p*,0.01) level of significance. Statistical software SYSTAT version-12 (by Cranes Software, Bangalore) was used.

## RESULTS

Out of the total 104 preterm babies, there were 37(35.58%) in 26–30 wk GA group, 37(35.58%) in 30–32 wk GA group and 30(28.84%) in 32–34 wk GA group. Distribution of birth weight-wise, maximum babies had birth weight between 1 and 1.5kg (17/37) in 26–30 wk GA group, whereas it was >1.5kg in other two groups 24/37 in 30–32 wk GA group and 19/30 in 32–34 wk GA group (Figure 1, Table 1).

Symptomatology-wise, neurological symptoms, viz., lethargy was commonest 13(35.13%) in 26–30 wk group. While CCF dominated in 30–32 wk group 22/37(5.4%) and 32–34 wk group 19/30(63.33%) (Table 2). A total of 26 out of a total 104 were asymptomatic but still received indomethacin as their PDA was hemodynamically significant. Associated heart defects seen in these babies were VSD (Small muscularand small, restrictive perimembranous VSDs) in three babies, ASD + VSD in three babies. Ionotropic support was needed in a total 10/104 babies. A total of nine babies required ventilation either as BIPAP or SIMV mode and all could be weaned of aventilator following ductal closure with indomethacin. A total of 75 (72%) PDAs closed with indomethacin while 13(12.5%) did not respond, and 16(15.38%) showed a reduction in the calibre of PDA (Table 3).26–30 wk group showed

**Table 1: Distribution of birth weight of baby (kg) according to gestational age**

| Birth weight of baby (kg) | Gestational age of babies in weeks (*n*=104) | | | |
|---|---|---|---|---|
| | 26–30 wk | 30–32 wk | 32–34 wk | Total |
| < 1 kg | 12(32.43%) | 2(5.40%) | 0 | 14(13.46%) |
| 1–1.5kg | 17(45.94%) | 11(29.73%) | 11(36.66%) | 39(37.5%) |
| > 1.5 kg | 8(21.62%) | 24(64.86%) | 19(63.34%) | 51(49.03%) |
| Total | 37 | 37 | 30 | 104 |
| Mean±SD | 1.51 kg±0.14 | 1.62 kg±0.18 | 1.81 kg±0.17 | 1.65 kg±0.22 |

Value of $x^2 = 19.19$, d.f.=6, significant, $p<0.05$.

**Table 2: Distribution of sign and symptoms according to gestational age**

| Sign and symptoms | Gestational age of babies in weeks | | | |
|---|---|---|---|---|
| | 26–30 wk (*n*=37) | 30–32 wk (*n*=37) | 32–34 wk (*n*=30) | Total (*n*=104) |
| No signs and symptoms | 11(29.72%) | 9(24.32%) | 6(20%) | 26(25%) |
| Congestive cardiac failure | 4(10.81%) | 22(5.40%) | 19(63.33%) | 45(43.26%) |
| Feeding problems | 9(24.32%) | 5(%) | 4(13.33%) | 18(17.31%) |
| Lethargy or poor activity (CNS manifestation) | 13(35.13%) | 1(2.70%) | 1(3.33%) | 15(14.42%) |

a brisk response to ductal closure with indomethacin within 108.1±12.44 hand a mean no. of cycles of indomethacin of 0.98±5.75.According to gestational age of baby, PDA was mostly open in premature baby less than 32weeks of gestational age (Table 4).

By applying Chi-square test there is a significant association between gestational age and birth weight of babies ($p$<0.05).

CNS manifestation here excluded IVH and lethargy or poor activity was attributable to PDA. As a protocol, all babies had a screening neurosonogram before administering indomethacin.

According to sign and symptoms, we found congestive cardiac failure was most common in 30–32 wk gestational age, while feeding difficulties & CNS manifestations were largely in 26–30 wk of gestational age baby.

Associated heart defects seen in these babies were VSD (small muscular and small, restrictive perimembranous VSDs) in three babies, ASD + VSD in three babies. Ionotropic support was needed in a total 10/104 babies. A total of nine babies required ventilation either as BIPAP or SIMV mode and all could be weaned of ventilator following ductal closure with indomethacin. A total of 75 (72%) PDAs closed with indomethacin while 13(12.5%) did not respond, and 16(15.38%) showed a reduction in the calibre of PDA.

By applying ANOVA test and Tukey–Kramer multiple comparison test there is a significant difference between mean initial dose, total no. of cycles, and response in time after administration in days ($p$<0.05).

## DISCUSSION

In fetal circulation, the ductusarteriosus channels blood from the pulmonary artery directly into the descending aorta. This enables about 90% of right ventricular output to bypass the unexpanded lungs [1]. At birth, functional closure of this channel redirects blood flow to the pulmonary vascular bed and allows the lungs to start effective respiratory gas exchange. Closure involves interaction of oxygen, prostaglandins, nitric

**Table 3: Distribution of complications of PDA and associated CHD, ventilator mode, inotropic support, and follow up 2D ECHO according to gestational age**

| | Gestational age of babies in weeks | | | |
|---|---|---|---|---|
| | **26–30 wk (*n*=37)** | **30–32 wk (*n*=37)** | **32–34 wk (*n*=30)** | **Total (*n*=104)** |
| Associated CHD | 1(3.33%) | –2(5.40%) | –1(2.70%) | 1 (0.96%) |
| ASD 5mm | –1(3.33%) | 1 (2.7%) | –1(2.70%) | 3 (2.88%) |
| ASD, VSD | 1(3.33%) | 1(2.70%) | | 2 (1.92% |
| PFO 3–4 mm | | | | 3 (2.88%) |
| VSD | | | | |
| Ventilator mode | 1(3.33%) | 2(5.40%) | 1(2.70%) | 4(3.85%) |
| BIPAP | 2(6.66%) | 2(5.40%) | 1(2.70%) | 5(4.81%) |
| SIMV | | | | |
| Inotropic support given | 2(6.66%) | 5(13.51%) | 3(8.11%) | 10(9.61%) |
| Follow up 2D ECHO | 3(10%) | 4(10.8%) | 6(16.21%) | 13 (12.5 %) |
| No PDA closure | 21(70%) | 29(78.38%) | 25(67.57%) | 75(72.1%) |
| PDA closed | 6(20%) | 4(10.81%) | 6(16.22%) | 16(15.38%) |
| PDA reduced in size | | | | |

**Table 4: Distribution of mean and SD values of initial dose, total no. of cycles, response in time after administration in days according to gestational age of babies**

| | Gestational age of babies | | |
|---|---|---|---|
| | **26–30 wk (*n*=37) Mean±SD** | **30–32 wk (*n*=37) Mean±SD** | **32–34 wk (*n*=30) Mean±SD** |
| Total number of cycles | 0.98±5.75 | 1.7±5.71 | 2.9±5.90 |
| Response in time after administration in hours | 108.10±12.44 | 125.00±16.78 | 128.08±19.63 |

oxide and the unique musculature of the ductus arteriosus. Indomethacin was introduced as an alternative to close the PDA. The purpose of this project is to explore the use of indomethacin as the first line of treatment for the closure of the PDA in the neonatal population.

In our study, we evaluated the effect of indomethacin in the management of PDA in the preterm neonates. Single or multiple indomethacin courses using the standard dosing approach resulted in high PDA closure rates for infants <34 weeks gestation.

In a study conducted by Gersony *et al.*, among 3559 newborn infants with birth weight <1750 g, 421 developing a hemodynamically significant PDA were entered into a randomized trial to evaluate the role of indomethacin in the management of PDA. Indomethacin given concurrently with usual medical therapy at the time of diagnosis resulted in ductal closure in 79%, versus 35% with placebo ($p<0.001$). Indomethacin as backup to usual medical treatment resulted in similar closure rates [7]. Our study demonstrated closure rate in 72% preterm babies.

The Cochrane review on the use of indomethacin in asymptomatic PDA, the reviewers concluded that there was a significant decrease in the incidence of symptomatic PDA following treatment of an asymptomatic PDA with indomethacin. There is also a small but statistically significant decrease in the duration of requirement for supplemental oxygen. There was no evidence on reduction in mortality, of IVH, CLD, ROP, or the length of ventilation [8].

Thus, though PDA closure benefits the baby acutely, long-term benefits are far from being achieved and more studies need to look at this perspective in a long-term follow up of preterm babies. Our study helped in weaning off the ventilator; however, whether this translated in prevention of BPD eventually was not studied.

A Cochrane database review showed no statistically significant difference in closure between ibuprofen and indomethacin [9]. A decision to use one drug versus another should be based upon the infant's presentation and comorbidities.

Our study looked at indomethacin only and ibuprofen was not tried in a single baby. A similar Cochrane database article that looked at the initial treatment of symptomatic PDA in preterm infants showed no difference in risks or benefits of surgery versus the use of cyclooxygenase inhibitors [10].

Chok *et al.* in their study on cerebral autoregulation in neonates with HS PDA found that cerebral autoregulation was better preserved after indomethacin treatment of an HS PDA compared with surgical ligation. Infants requiring surgical HS PDA ligation may be at increased risk for cerebral pressure passivity in the 6 h following surgery [11].

None of the nonresponders in our group were subjected to surgical ligation due to resource limited settings of rural hospital.

## CONCLUSIONS

Indomethacin a non-selective COX inhibitor is a time-tested drug in the closure of preterm ductus and in the present study achieved 72% (75/104) closure rates with indomethacin. Although 29/104(27.88%) PDAs did not

close, a good 15.38% (16/104) PDA reduced in calibre on sequential echo studies demonstrating the effectiveness of indomethacin.

Surgical ligation is feared for complications, viz., clylothorax, vocal cord palsy, pneumothorax; besides increasing the sepsis rates in preterm babies and was not attempted in our study.

The best response to indomethacin was noted in 30–32 wk GA group, demonstrating the prostaglandin sensitivity of these preterm babies, while maximum nonresponders were in 32–34 wk; suggesting as gestation increases, response to PG inhibitors decreases.

### Limitations of the Study

We did not compare indomethacin with ibuprofen or paracetamol which are relatively safer drugs in terms of nephrotoxicity. Surgical ligation or catheter-based intervention, viz., PDA-coil occlusion was not attempted in nonresponders to indomethacin. Long-term benefits of early PDA closure, viz., prevention of CLD, ROP, morbidity, neuro developmental outcome were not studied.

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