Original Research Article

Paracetamol vs Ibuprofen in Patent Ductus Arteriosus (PDA) in preterms: a randomized controlled trial

Abstract:

Background and Objective

Hemodynamically significant patent ductus arteriosus (HsPDA) is a common cause of morbidity in preterm infants. Closure of the ductus can be done with either Indomethacin or Ibuprofen, which are cyclo-oxygenase (COX) 1, 2 inhibitors. As, Ibuprofen has several contraindications, a trial of oral paracetamol (a peroxidase inhibitor), with ibuprofen, was designed to compare the efficacy and safety of oral paracetamol vs oral ibuprofen for the pharmacological closure of HsPDA in preterm infants.

Methods

140 infants (gestational age <32 weeks) with echocardiographically confirmed HsPDA were randomly assigned to receive either oral paracetamol (70) or ibuprofen (70). After initial treatment course in both the groups, the need for a second course was determined by echocardiographic evaluation. The rates of ductal closure, adverse effects of drugs, discharge rate were documented.

Results

Rate of ductal closure was similar in both groups after first course (p=0.46) and second course (p=0.59). However, 22 from Ibuprofen group and only 2 from PCM group developed adverse effects (p<0.001). From paracetamol group 58 were discharged, and 12 died; while from ibuprofen group 46 discharged, 24 died (p=0.03).

Conclusion

Paracetamol for HsPDA in preterm neonates was associated with good efficacy and better safety; and less deaths, as compared to ibuprofen.

Introduction

Hemodynamically significant patent ductus arteriosus (hsPDA) is a major morbidity seen in premature infants, with its incidence being inversely related to gestational age. Studies report incidence of 15-40% in very low birth weight infants (<1500g) whereas in premature extremely low birth weight infants (<1000g) it is as high as 50-65%.[1,2] The ductus arteriosus functionally closes in term infants by 12-24 hrs, whereas the closure may be delayed by 3-4 days in preterm infants.[3] Clinical signs of patent ductus arteriosus (PDA) usually appear later than echocardiographic signs.[4] Patent ductus arteriosus is associated with several neonatal morbidities like metabolic acidosis, necrotizing enterocolitis (NEC), and pulmonary oedema/haemorrhage.

Closure of the ductus arteriosus occurs in two phases: (1) “functional” closure of the lumen by smooth muscle constriction, within hours after birth; (2) “anatomic” occlusion of the lumen over the next several days, due to neointimal thickening and loss of smooth muscle cells from the inner muscle media.

The most important mechanism that prevents the preterm ductus from constricting after birth is its increased sensitivity to the vasodilating effects of prostaglandin E2. As a result inhibitors of prostaglandin production (e.g. indomethacin, ibuprofen) are used for ductal closure.[5]

Treatment for closure of hsPDA includes pharmacological therapy and surgical ligation. Indomethacin and ibuprofen, both inhibit the conversion of arachidonic acid to prostaglandins by COX inhibition, are the two most commonly used drugs for closure of PDA.[6]

Studies conducted on ibuprofen for treatment of PDA shows successful closure of hsPDA in 70%–85% of cases.[7] However, several serious adverse effects have been reported with both indomethacin and ibuprofen, which include intense peripheral vasoconstriction, gastrointestinal bleeding and perforation, decreased platelet aggregation, Hyperbillirubinemia, renal failure.[8,9] When drug treatment fails clinician may resort to surgical intervention of symptomatic PDA in preterm infants, and the risk of complications (post ligation hypotension, bronchopulmonary dysplasia, vocal cord paralysis, neurodevelopmental abnormalities) from the operation is high.

Paracetamol, unlike ibuprofen, acts on prostaglandin synthase by peroxidase inhibition. Few studies have been conducted on paracetamol treatment of PDA in preterm newborns till date. Therefore, we conducted a randomized, controlled trial in order to compare oral paracetamol and ibuprofen for hsPDA closure in premature infants.

Material and method

In this prospective randomized, non blinded study, we obtained written informed consent from parents to enrol LBW preterm infants (Less than 32 weeks gestational age; Birth weight ≤ 1250 g; 2D Echo suggestive of HsPDA -Hemodynamically significant PDA) admitted to the neonatal intensive care unit at the Sir T G Hospital, Bhavnagar, Gujarat. The study was approved by IRB (Institutional Review Board) / HEC (Human Ethics Committee) of Govt. medical college, Bhavnagar. Infants with Major congenital anomalies, right-to-left ductal shunting and persistent pulmonary hypertension, liver dysfunction excluded.

Sample size: Total 140 patients were studied after considering inclusion and exclusion criteria. (Flow chart)

Enrolment process: From Feb 2018 to August 2018, 167 preterm, low birth weight infants were enrolled in study, of which 27 were excluded (Flowchart figure 1). Recruitment was continued till 140 patients were completed; as in group A four and group B three patients expired prior to completion of trial, so another seven patients were enrolled.

Intervention and comparison groups

Intervention

Paracetamol oral suspension [Paracetamol syrup, 50 ml; (125 mg/5 ml) Adman Formulations] administered through orogastric tube at a dose of 15 mg/kg/dose at six hourly intervals for three consecutive days.

Active control

Ibuprofen oral suspension [50 ml (100 mg/5 ml) Riemann Labs PL] administered through orogastric tube at a dose of 10 mg/kg/dose and 5 mg/kg/dose after 24 and 48 hours from the first dose.

Both the drugs would be filled in 5 ml plastic syringes and gently pushed through the orogastric tube followed by a flush of 1 ml of sterile water for injection.

Study methodology:

The participants were randomly assigned at a 1:1 ratio between oral paracetamol and ibuprofen groups by using cards in sealed opaque envelopes. And doctors and nurses were not blinded. Data regarding age, sex and clinical condition related with PDA collected as baseline information. 140 infants (gestational age ≤32 weeks) with echocardiographically confirmed PDA were randomly assigned to receive either oral paracetamol (n = 70) or ibuprofen (n = 70). Group A (Acetaminophen group) was treated with syrup Paracetamol and Group B (Brufen group) was treated with syrup Ibuprofen as per above given dosage and formulation. Echocardiographic assessments would be done after completion of the course or until the closure of the PDA, whichever is earlier. PDA would be considered as closed after confirmation with 2Decho. Whether a subject received a second course of treatment depended on echocardiography evaluation after the first course. If only minor ductal shunting was present after two courses without the need of respiratory support, no further treatment was given. Patients were assessed daily during the treatment, including 24-h urine output, bleeding tendency, intracranial haemorrhage (ICH), and renal function test and bilirubin levels. The occurrence of any of the following conditions would prompt the stopping of treatment: renal failure, NEC (necrotising enterocolitis), ICH (intracranial haemorrhage) grade 3–4, gastrointestinal bleeding.

Outcome measurement

The main outcome was rate of ductal closure, and secondary outcomes were adverse effects and complications and discharge rate. Secondary outcome of expiry was assessed at the end of treatment.

Statistical Analysis

A study group of 140 patients was needed to detect a difference of at least 20% in the closure rate between the oral paracetamol and ibuprofen groups, assuming a closure rate of 70% with oral ibuprofen, with a 95% confidence interval (CI) and a power of 80%. Anticipating that a few patients could be excluded due to various causes during the study, interim analyses were performed for main and secondary outcomes at 50% recruitment. The study would be terminated if a difference of 20% in the main outcome or a significant increase in the secondary outcome. Continuous data were given as means. Differences between groups were determined by the t test for parametric continuous data, χ^2 for categorical data. All statistical tests were two-sided and $p < 0.05$ was considered statistically significant.

Statistical software: The Statistical software namely IBM SPSS was used for analysis of the data and Microsoft word and Excel have been used to generate graphs, tables.

Observations and Results:

From Feb 2018 to August 2018, 167 preterm, low birth weight infants were enrolled in study, with an average gestational age of 29.5 weeks and average birth weight 1.15kg. From this 16 preterms having congenital anomalies, and 8 patients, not meeting inclusion criteria were excluded. Three patients Expired prior to trial. Few patients expired during the study were excluded, 140 patients in total were enrolled in each group.

Demographic data: (Table 1)

Out of total 140 patient studied, 28 (20%) were <1kg and 112 (80%) were between 1-1.5 kg. Total 73 were male and 67 were female. 78 preterms were born by NVD and 62 by LSCS. Mean birth weight in Group A and Group B was 1.15 ± 0.950 and 1.12 ± 0.115 respectively, Gestational age of Group A and Group B was 29.7 ± 1.67 and 29.3 ± 1.38. In our study antenatal steroids were given to total 79 preterms, out of which 42 were in Group A and 37 were in group B In this study there is no statistical significance in all demographic data mentioned in Table 1. So both groups were comparable for that.

As shown in Table 2, the ductus was closed in 51 (73%) patients of paracetamol group (A) compared to 46 (65%) patients of ibuprofen group (B) after 1st course, and there was no significant difference between the two treatments ($p = 0.46$). Size of PDA decreased in 15 (22%) of group A and 17 (24%) of group B ($p=0.84$). Four patients of group A and 7 patients of group B had no change in size of PDA after 1st course ($p=0.53$).

As per table 3, total 37 patients required 2nd course of treatment. Three patients of group A and B had tiny hemodynamically not significant PDA. So, they did not receive 2nd course. After the 2nd course, PDA completely closed in 10 (63 %) patients of Group A as compared to 16 (76 %) of Group B (p=0.59). There is no significant difference for 2nd course of treatment between both groups.

There was no change in size of PDA in five patients of Group A and five patients of group B after two course of therapy (p=0.90).

As per Table 4, side effects were observed in 22 (31%) patients treated with Ibuprofen as compared to 2 (3%) patients treated with paracetamol. There is significant difference in side effects of drug between both groups (*p< 0.001*). Paracetamol has lesser side effects than ibuprofen, so it is safer drug than ibuprofen.

As per table 4, out of 70 patients 58 were discharged and 12 patients expired from group A. While, in group B total 46 patients were discharged and 24 patients expired (*p=0.03;* significant difference). Out of 36 expired patients 21 were male and 15 female.11 patients expired after 2nd course (4-PCM group, 7-Ibuprofen group).

Discussion

Demographic Data

Gestational age in Mean ± SD of Group A and Group B was 29.7± 1.67s and29.31. ± 38 respectively, so both Groups were comparable as difference between groups was not statistically significant (p =0.18).

In a study conducted by Dang D,[10] mean gestational age in Ibuprofen group was 30.9± 2.2 and Paracetamol group was 31.2± 1.8.

Primary closure

In a study done by Dang D, After the 1st course of treatment, ductal closure occurred in 45 infants (56.3%) given paracetamol and in 38 infants (47.5%) administered ibuprofen (p= 0.268).[10] In another study done by Oncel M, after the first course of treatment, the PDA closed in 31 (77.5%) of the patients assigned to the oral ibuprofen group vs. 29 (72.5%) of those enrolled in the oral paracetamol group (*P* =0.6).[11] Similarly, in our study there was no significant difference found between the two treatments (p = 0.46) [table 1].

Secondary closure

In study done by Oncel M, The cumulative closure rates after the second course of drugs were high in both groups. Only 2 patient (2.5%) in the paracetamol group and 3 patients (5%) in the ibuprofen group required surgical ligation.[11]

In a study done by Dang D, secondary closure rate was 20 (25%) of Paracetamol group as compared to 25 (31.3%) of Ibuprofen Group. There was no significant difference for 2nd course of treatment between two groups (p=0.38).[10]

In our study after two courses, Total 6(8%) patients of Group A and 5 (7%) patients of Group B required surgical ligation (table-3)and no significant difference for 2nd course of treatment between two groups (p=0.89).

Adverse effect

In the study by Dang D, There were no significant differences between the two groups in the incidence of oliguria, renal failure, NEC, ICH grade. However, differences in the incidence rates of gastrointestinal bleeding and Hyperbillirubinemia between the two groups were significant (P= 0.05).[10] In our study there was significant difference in side effects of drug between two groups (*p< 0.001*) (Table 4).

Another study by, Sinha R, reported an interesting findings of ductal closure in 10 preterm neonates (gestational age 27-33 wks) presenting with significant large PDA who had failed or had absolute contraindication with Brufen. These preterm neonates were treated with oral paracetamol in the dose of 15 mg/kg 8 hourly. The PDA closure was achieved within 48 h and there was no complication.[12]

A study by, Hammerman C, in which 5 preterm were studied who had contraindication to ibuprofen, Ductal closure was achieved within 48 hours in all the treated infants with Paracetamol. No adverse event was observed.[13]

As per table 4, after completion of treatment, out of group A of 70 patients, 58 were discharged and 12 expired. While from group B, 46 were discharged and 24 expired. There was significant difference in discharge rate of both groups (*p=0.03*).

This may be because more patients required 2nd course of treatment in ibuprofen group as compared to paracetamol leading to longer stay in hospital. Additionally, there was higher rate of side effects in ibuprofen group B.

A Cochrane review[14] about paracetamol for PDA in pre-term and VLBW infants concluded that further follow-up trials for the long term safety of paracetamol should be conducted; as concerns have been raised regarding the development of autism or autism spectrum disorder (ASD) in childhood after prenatal and postnatal exposure to paracetamol.

The supposedly increased incidence of ASD from 3.9 to 5.6:1 boy: girl [15] with postnatal paracetamol usage, Circumcision rates are presented as a proxy for an early male neonatal exposure to paracetamol in one study.[15]

In this study only boys were studied so there was selection bias. The timeline for the actual implementation of child pain management protocols and the utilization of paracetamol with circumcision is not known. Additionally, pain management guidelines suggest that paracetamol alone is not sufficient to manage circumcision pain so a nerve block or local anaesthesia may also be administered, which may be confounding factors. The assumption that paracetamol use for neonatal circumcision pain leads to more ASD incidence is not without significant limitations.[15] In general, this type of ecologic study has significant limitations that severely limit causal inference.[15] The effect of paracetamol association with Autism causation should be studied in male neonates, either with or without paracetamol usage in communities in circumcision procedure.

Conclusion

This randomized, controlled trial compared oral paracetamol with oral ibuprofen in preterm infants, and primary and secondary closure rate for the closure of hemodynamically significant patent ductus arteriosus, was comparable in both groups, with minimal side effects of paracetamol even after two course of treatment. Paracertamol group had no risk of gastrointestinal bleeding, Hyperbillirubinemia, NEC, ICH, oliguria and had less mortality as compared with ibuprofen treatment.

Recommendation

Paracetamol should be considered as a new alternative treatment for PDA in preterm newborns for HsPDA with good efficacy, better safety and, less mortality as compared to ibuprofen.

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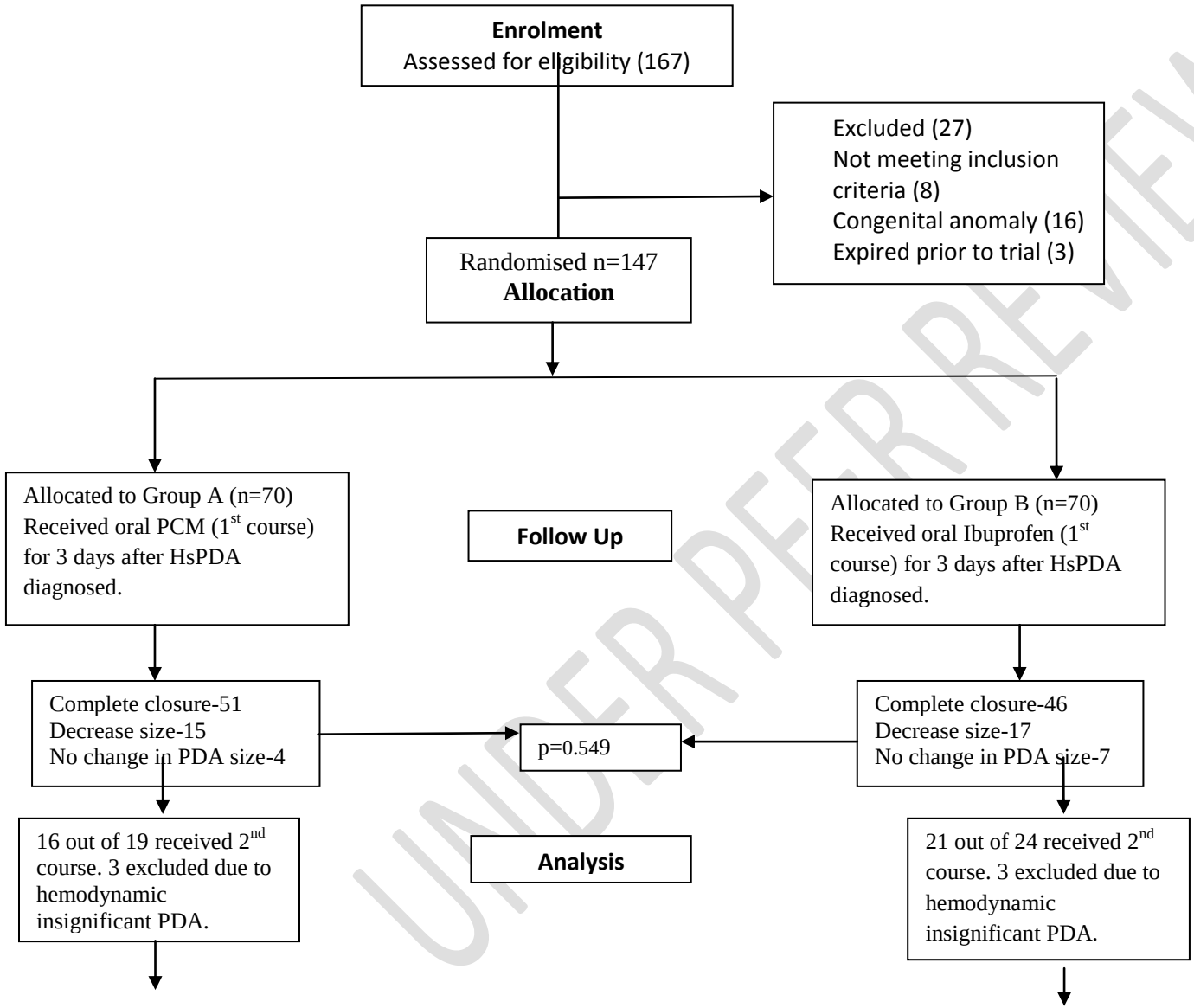
Figure 1: Flowchart- Allocation and outcome



Complete closure-10
Decrease size-1
No change in PDA size-5

p = 0.419

Characteristic	Group A (n=70) Paracetamol	Group B (n=70) Ibuprofen	p value
Gender	Male- 36 Female- 34	Male- 37 Female- 33	0.86
Mode of delivery	NVD- 42 LSCS- 28	NVD- 36 LSCS- 34	0.30
Birth weight	1.15 ± 0.950	1.12± 0.115	0.11
Gestational Age	29.7± 1.67	29.3± 1.38	0.18
Antenatal steroid	42	37	0.39

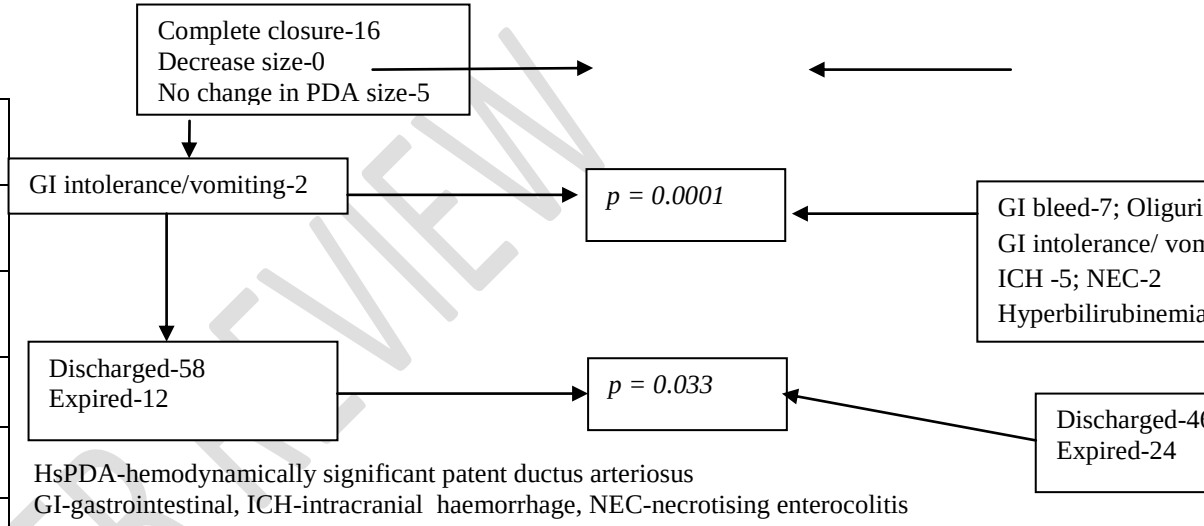


Table 1: pre-intervention characteristic of both groups

NVD-normal vaginal delivery, LSCS-lower segment caesarean section

Table 2: Primary closure of PDA after first course: n (%)

PDA outcome, n	**Group A (n = 70)**	**Group B (n = 70)**	**p value**
Complete closure (97)	51 (73)	46 (65)	0.46
Decreased size (32)	15 (21)	17 (25)	0.80
No change (11)	4 (6)	7 (10)	0.52

Table 3: Closure of PDA after second course: n (%)

PDA outcome, n	**Group A (n = 16)**	**Group B (n = 21)**	**p value**
Complete closure, 26	10 (62)	16 (76)	0.58
Decreased size, 1	1 (6)	0	-
No change, 10	5 (32)	5 (24)	0.89

Table 4: Side effects and deaths

Complication/ Outcome	**Paracetamol Group A n =70 (%)**	**IBuprofen Group B n = 70 (%)**
GI bleed	-	7 (10)
GI intolerance/vomiting	2 (3)	3 (4)
NEC	-	5 (7)
IVH	-	2 (3)
Hyperbillirubinemia	-	2 (3)
Oliguria	-	3 (4)
Total*	2 (3)*	22 (31)*
Deaths#	12 #	24 #

GI-gastrointestinal, NEC-necrotising enterocolitis, ICH- intracranial haemorrhage
**p = 0.0001; #p = 0.033*