Paracetamol vs Ibuprofen in Hemodynamically Significant Patent Ductus Arteriosus (HsPDA) 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. Indomethacin and Ibuprofen, which are cyclo-oxygenase (COX) 1, 2 inhibitors are commonly used drugs for closure of HsPDA. As, Ibuprofen has several contraindications, we designed study using oral paracetamol (a peroxidase inhibitor) and compared with oral ibuprofen, for efficacy and safety in relation to closure of HsPDA in preterm infants.

Methods

140 preterm infants (gestational age less than 32 weeks) with HsPDA (confirmed by 2D Echo) were randomly assigned in two groups and received first course of either oral paracetamol (70) or ibuprofen (70). The need for a second course was determined by 2D Echo evaluation. Parameters studied were rate of ductal closure, any adverse effects and discharge rate.

Results

Both groups were similar in term of ductal closure 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.

Keywords: Patent ductus arteriosus, Paracetamol, Ibuprofen, Preterm.

Introduction

Hemodynamically Significant Patent Ductus Arteriosus (HsPDA) is a cause of major morbidity in preterms. Incidence of which is inversely related to gestational age. HsPDA is seen in 15-40% in infants <1500g and as high as 50-65%. in infants <1000g, as per described literature. [1,2] The functional closure of ductus arteriosus occurs by 12-24 hrs in term infants,

but it may be delayed by 3-4 days in preterms.[3] Usually clinical signs of HsPDA appear later than echocardiographic signs.[4] Several neonatal co-morbidities such as necrotizing entero-colitis, metabolic acidosis, pulmonary oedema/haemorrhage, intracranial haemorrhage etc. are associated with PDA, but causative association is still unclear.

In normal circumstances, the ductus arteriosus closure occurs first functionally by constriction of smooth muscle (within few hours after birth) and then anatomically by loss of smooth muscle cells in the inner muscle media and thickening neointima (over the next several days).

The increased sensitivity of preterm ductus to the vasodilating effects of prostaglandin E2 is the most important factor, preventing its constriction after birth[i]. 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]
Successful closure of HsPDA has been seen in 70%–85% with the treatment by Ibuprofen. [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 consider surgical intervention for HsPDA, but the surgical risks like post ligation hypotension, vocal cord paralysis, bronchopulmonary dysplasia, neurodevelopmental abnormalities remain high.
Paracetamol, unlike ibuprofen, acts on prostaglandin synthase by peroxidase inhibition. Few studies assessing use of paracetamol in treatment of HsPDA in preterms have been conducted till date. For comparing oral paracetamol vs ibuprofen in closure of HsPDA in preterms, we conducted a randomized, controlled trial at our institution after getting approval from IRB (Institutional Review Board) / HEC (Human Ethics Committee).

Material and method

In this prospective randomized, non-blinded study, we obtained written informed consent from parents to enrol LBW preterm infants with inclusion criteria of

- gestational age less than 32 weeks;
- Birth weight ≤ 1250 g

- 2D Echo suggestive of HsPDA
- admitted to the neonatal intensive care unit at our hospital.

Infants with major congenital anomalies, right-to-left ductal shunting and persistent pulmonary hypertension, liver dysfunction were excluded.

Sample size: Total 140 patients were studied after considering inclusion and exclusion criteria. (Figure 1)

Enrolment process: From Feb 2018 to August 2018, 167 preterm, with birth weight ≤ 1250 g were enrolled in study, of which 27 were excluded. 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:

Subjects were randomly assigned between two groups (oral paracetamol vs. oral ibuprofen, 1:1 ratio) by using cards in sealed opaque envelopes. Blinding was not done for doctors and nurses. Data regarding age, sex and clinical condition related with PDA collected as baseline information. 140 preterm infants with HsPDA confirmed by 2D Echo 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 either after completion of the suggested course or until the

closure of the HsPDA, whichever is earlier. PDA would be considered as closed after confirmation with 2D Echo. Whether a second course of treatment to be given to subject depended on evaluation by 2D Echo after the first course. No further treatment was given if after two courses, only minor ductal shunting was present and there would not be any need of respiratory support. During the treatment, detailed daily assessment was done, including 24-h urine output, bleeding tendency, intracranial haemorrhage (ICH), and renal function test and bilirubin levels. Treatment was promptly stopped with occurrence of any of the following conditions: renal failure, NEC (necrotising enterocolitis), ICH (intracranial haemorrhage) grade 3–4, gastrointestinal bleeding.

Outcome measurement

The primary outcome of our study was rate of closure of HsPDA whereas adverse effects/complications and discharge rate were secondary outcome. Detailed assessment of patients expired during study was done at the end of treatment.

Statistical Analysis

Assuming a closure rate of 70% with oral ibuprofen, 140 subjects were required to detect minimum 20% difference in the closure rate between the two groups, with a 95% confidence interval (CI) and a power of 80%. Interim analyses were performed at 50% recruitment, with anticipation of having exclusion of few subjects during the study. The study would be terminated either in case of having a difference of 20% in the primary outcome or a significant increase in the secondary outcome. Representation of continuous data were given as means. The two groups were compared using student's 't test' for parametric continuous data and χ^2 for categorical data, considering $p < 0.05$ as 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 infants were assessed for enrolment in trail, 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 enrollment in 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. Group A and Group B, mean birth weight was 1.15 ± 0.950 and 1.12 ± 0.115 respectively, whereas gestational age 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 closure of HsPDA after 1st course of treatment was observed in 51 cases (73%) of group A and 46 cases (65%) of group B (difference not statically significant,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. The closure of HsPDA after 2nd course of treatment was observed in 10 cases (63 %) of Group A and 16 cases (76 %) of Group B (difference not statically significant, p=0.59). 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 in each group, 12 patients expired from group A and 24 patients expired from group B (*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

As per described in study by Dang D et al, rate ductal closure after the 1st course of paracetamol treatment was 56.3% (45 infants) whereas in ibuprofen subgroup rate was 47.5% (38 infants) (p= 0.268).[10] Oncel M in his study showed, rate of PDA closure to be 72.5% (29 infants) with paracetamol vs 77.5%(31 infants) with oral ibuprofen group (*p* =0.6).[11] We also could not find any significant difference between the two treatments in our study (p = 0.46) [table 1].

Secondary closure

Oncel M et al showed good cumulative closure rates after the second course treatment in both groups. In his study, surgical ligation was required in 2 patients (2.5%) of paracetamol group and 3 patients (5%) of ibuprofen group.[11]

Dang D et al did not found significant difference in secondary closure rates in Paracetamol (25% ,20 cases) and Ibuprofen Group 31.3% (25 cases). (p=0.38)

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, two groups were similar with relation to the incidence of oliguria, NEC, renal failure, ICH etc. However, incidence of gastrointestinal bleeding and Hyperbillirubinemia were significantly higher with ibuprofen (p= 0.05).[10] In our study, adverse effects of Paracetamol group was significantly lower than Ibuprofen. (*p< 0.001*) (Table 4).

Sinha R et al, used oral paracetamol in the dose of 15 mg/kg 8 hourly for cases of gestational age 27-33 weeks presenting with significant large PDA (with absolute contraindication/ failed treatment with Brufen) and reported ductal closure within 48 h in 10 preterms without any complication.[12]

Hammerman C et al, also achieved ductal closure within 48 hours with paracetramol without any reported adverse event in 5 preterm presenting with HsPDA and having contraindication to ibuprofen.[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. Thus, Paracetamol group was having higher discharge rate (*p=0.03,* difference statistically significant).

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. One study has presented circumcision rates as a proxy for neonatal exposure to paracetamol in males.[15] This study had selection bias as only male patients were included. The data regarding historic implementation and actual timeline for child pain management protocols as well as utilization of paracetamol in circumcision is very confirmatory. Additionally, paracetamol alone being not enough to manage pain in circumcision procedure, nerve block/ local anaesthesia may be used additionally, which may work as confounding factors. Thus, there are significant limitations in concluding the assumption regarding use of paracetamol in neonatal circumcision and its causative association with more ASD incidence.[15] Association of paracetamol with Autism as causative factor should be studied in more details in communities undergoing circumcision procedure in male neonates.

Conclusion

Oral paracetamol is as effective as oral ibuprofen for the closure of hemodynamically significant patent ductus arteriosus. Our randomized, controlled trial showed primary and secondary closure rate to be comparable in both groups. Also, side effects with even two courses of paracetamol treatment are minimal with less mortality in comparison 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

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[ii]

Table 1: Pre-intervention characteristic of both groups

Characteristic	**Group A (n=70)**	**Group B (n=70)**	**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

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*