Section: Pediatrics

Original Research Article

PROPHYLACTIC INTRAVENOUS PARACETAMOL FOR PREVENTING MORTALITY AND MORBIDITY IN PRETERM VERY LOW BIRTH WEIGHT NEONATES: A RANDOMIZED CONTROL TRIAL

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Abstract

Background: During the fetal life, ductus arteriosus facilitates blood circulation between the aorta and pulmonary artery. After birth, the ductus arteriosus closes, but remains patent in 60% of preterm neonates. Though paracetamol is an effective, novel drug with exceptional safety profile in neonates for closure of PDA, consensus on its timing of administration has not been met, which is the focus of this trial. Aims: Primary:• To determine the effect of prophylactic paracetamol for PDA closure on mortality and morbidity in preterm very low birth weight neonates. Secondary: • To study the efficacy of intravenous paracetamol when used for PDA closure in preterm very low birth weight neonates within 24 hours of life. • To study any adverse events following paracetamol therapy and to delineate its therapeutic outcome in reducing the incidence of intraventricular haemorrhage, necrotising enterocolitis, retinopathy of prematurity, bronchpulmonary dysplasia and shock among the preterm very low birth weight neonates. • To compare the effect of early paracetamol (within 24 hours) for PDA closure with routine paracetamol usage following clinical PDA. **Materials and Methods:** This trial was undertaken to assess whether early administration of paracetamol can reduce mortality and morbidity in preterm, VLBW neonates. This was an open label randomized controlled trial conducted at Coimbatore Medical College Hospital between March 2021 and June 2022. 84 neonates with gestational age <34 weeks and birth weight <1.5kg were recruited and randomly assigned to intervention and standard treatment groups. Neonates in the intervention group received 10mg/kg paracetamol Q8H for 3 days while those in the standard treatment group received treatment as per unit protocol. **Result:** Cumulative data analysis showed no significant difference in mortality (p = 0.301). However, incidences of shock, sepsis, IVH, ROP, pulmonary congestion, requirement of mechanical ventilation, ductal diameter on day 3 reduced in the intervention group. Further stratification and subgroup comparison revealed significant results for shock, pulmonary congestion, IVH, ROP, ductal diameter on day 3, requirement of mechanical ventilation among the neonates weighing 1-1.25 kg. **Conclusion:** Paracetamol when administered as prophylactic drug has been observed to cause reduction in the morbidity among preterm, very low birth weight neonates, especially in the birth weight category of 1-1.25kg.

INTRODUCTION

Patent ductus arteriosus (PDA) is a serious morbidity of preterm neonates predominantly in neonates less than 1000g birth weight or less than 28 weeks gestation with rate of incidence 50 – 65 % and 15 - 40% in neonates less than 1500g birth weight.[1-4] The ductus arteriosus is the communication between the pulmonary artery and aorta which is necessary for fetal circulation.[5] During fetal life, since fetal pulmonary vascular resistance is high, nearly 90 % of blood ejected by the fetal right ventricle flows

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through ductus arteriosus to descending aorta and thereafter to other systemic vessels and culminating in the umbilical vein.[6] After fetal to neonatal transition, spontaneous closure occurs within 72 hours of life.[7] At birth increased oxygenation and reduced flow through ductus arteriosus facilitate the closure of ductus by mediating a shift in balance between the vasodilating PGE2 mediators and vasoconstricting endothelin. However in preterm neonates the reduced intrinsic vascular tone due to weak actin myosin complex formation, elevated levels of PGE2, increased PGE2 receptors and reduced oxygen sensitivity of the endothelial smooth muscle layer delay this process.[8]

The fall in pulmonary vascular resistance allows the blood flow to lung for oxygenation. In two third of preterm neonates, spontaneous closure of the ductus take place. This spontaneous closure of ductus arteriosus gets delayed with decreasing birth weight and gestation, leading to low rate of spontaneous closure.[9]

A Patent Ductus Arteriosus shunts blood from systemic to pulmonary circulation When hemodynamically significant, this excessive blood flow to lungs leads to pulmonary congestion and increased respiratory support. Also the incidence of intraventricular hemorrhage is increased due to alteration of cerebral perfusion pressure. The inadequate blood flow to other vital organs leads to hemodynamic instability, shock, necrotizing enterocolitis etc.[10-12]

To reduce the incidence of morbidity and mortality in preterm very low birth weight neonates closure of the patent ductus has been tried using many pharmacological agents.[13] Pharmacological management includes the use of non- steroidal anti-inflammatory drugs- ibuprofen,[14] and indomethacin,[15] which act by inhibiting prostaglandin synthesis by acting on the cyclooxygenase pathway. The rationale behind inhibiting prostaglandin,[16] synthesis lies in the fact that high levels of prostaglandin result in vasodilatation and smooth muscle relaxation which thereby contributes to ductal patency and other complications. But exposure to these medications puts the vulnerable preterm neonates at risk of feed intolerance, necrotising enterocolitis, intestinal perforation, nephrotoxicity and cerebral injury. Another novel drug in use which also acts by hindering prostaglandin synthesis by selectively inhibiting the cyclooxygenase 2 pathway (COX 2) is paracetamol which has excellent efficacy and safety profile.[17]

The role of paracetamol,[18,19] as an alternative treatment for closure of hemodynamically significant PDA has gained attention in recent years because of its excellent safety profile in comparison to other cyclooxygenase inhibitors.[20-22]

Several recent observational studies and randomised controlled trial (RCT) studies,[23-25] show that paracetamol may be as effective as ibuprofen and indomethacin for closing PDA in preterm infants . However evidence regarding the indications, dosage, effectiveness, and safety profile including the long-term effects of paracetamol are still incomplete or lacking.[26]

The appropriate management of patent ductus arteriosus is highly controversial regarding the need to treat, medication to be used and timing of pharmacotherapy. Hence this study is undertaken to experiment if prophylactic administration of paracetamol within 24 hours of life in preterm very low birth weight neonates has efficacy in reducing the incidence of mortality and morbidity .

MATERIALS AND METHODS

Study design: This is a prospective, open label, parallel, single centered randomized control trial.

Study period: May 2021 and April 2022.

Study population: The neonates with gestational age less than 34 weeks and birth weight less than 1.5 kg admitted in the SNCU.

Inclusion Criteria

- Neonates < 34 weeks gestation
- Birth weight <1500 g
- Ductus Arteriosus diameter >1.5 mm (bedside ECHO)

Exclusion Criteria

- The neonates with major congenital anomalies
- Severe birth asphyxia (APGAR score <4/10 at 5 minutes of life)
- Duct dependent cardiac anomalies
- Abnormal liver function tests were excluded

The sample size is calculated with a non-inferiority margin of 0.1 at a power of 80%, the details are given in Table 1.0.

Local ethical committee approval obtained. 120 neonates were admitted in the SNCU of Coimbatore Medical College Hospital of which 84 neonates met the inclusion criteria. Parents of all the neonates included in the study were explained about the methodology and investigations and written informed consent obtained.

Randomization: The neonates were stratified into three categories based on birth weight (< 1kg, 1 to 1.25 kg and 1.25 to 1.5 kg). Block randomization was done and random number table generated. Allocation concealment was carried out using sealed opaque envelopes. Neonates were randomized into two groups: intervention group (n=42) and control group (n=42). Prophylactic paracetamol was administered in the intervention group and standard treatment protocol was followed in the control group.

Intervention:

- A routine history taking, physical examination of the cardiovascular and respiratory system was performed.
- Baseline blood investigations with bedside screening neurosonogram and echocardiogram were done on day 1.
- Chest X ray was taken in neonates with respiratory distress requiring oxygen support. Neonates

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allocated to the intervention group received intravenous paracetamol at a dose of 10mg/kg every eight hours within first 24 hours of life according to defined birth weight criteria for 3 days.

- The neonates in the control group were observed for signs and symptoms of hemodynamically significant PDA (hsPDA). A bedside echocardiogram was done in 72 hours of life or earlier if signs of hsPDA were present. If present, the neonates received intravenous paracetamol 10mg/kg every 8 hours for 3 days.
- Respiratory distress (Downe's score) was monitored at admission, 12 hours and 24 hours
- Bedside ultrasound cranium was performed at day 3, day 7, day 14 and day 28 as per unit protocol
- The neonates in both groups were observed for shock, feed intolerance, sclerematous changes and abnormal vitals. If any or all the symptoms were present, a complete blood count, C-reactive protein and blood culture sensitivity were done to confirm the same.
- If the neonate had new onset tachypnea/respiratory distress, a chest X ray was carried out to find evidence of pulmonary congestion.
- The number of days of oxygen support required by the neonate and the type (mechanical ventilation, CPAP ventilation and HFNC ventilation) were observed.
- Baseline Liver function tests were conducted at admission and serially to observe for liver injury.
- All the neonates, in the intervention and control groups, underwent fundus examination by the ophthalmologist to look for retinopathy of prematurity (ROP).

Baseline maternal factors (anemia, pregnancy induced hypertension, gestational diabetes, hypothyroidism, prolonged rupture of membranes, amniotic fluid volume, prenatal steroid administration, type of delivery) and neonatal factors (gestational age, birth weight, sex, delivery room resuscitation and admission Downe's) were analyzed and are represented as tables 2.0 and 3.0.

Primary outcome: To compare the rate of mortality between the study groups.

Secondary outcomes: The incidence of the following factors are studied:

- Shock
- Sepsis
- Hypoglycemia
- Pulmonary congestion
- Feed intolerance
- Elevated liver parameters
- Internal diameter of the ductus arteriosus >1.5 mm on day 3
- Intraventricular hemorrhage (IVH)
- Bronchopulmonary dysplasia (BPD)
- Retinopathy of prematurity (ROP)
- Requirement of mechanical ventilation
- Requirement of CPAP ventilation
- Requirement of HFNC ventilation
- Duration of stay in level 3
- Duration of hospital stay

The research design is presented in consort flow diagram (Figure 1.0)

Statistical analysis: The data was collected using Epi Info, processed in Excel and analysed by SPSS software 16.0. Categorical variables were presented as frequency and percentages and continuous variables as Mean / Median ± Standard deviation. Association between categorical variables was examined using Chi square / Fischer exact. The association between continuous variables between both groups were measured by T-test / Mann Whitney U test/ Kruskal Wallis test. Inferences were drawn for P values with <0.05 as statistically significant.

RESULTS

The baseline maternal and neonatal characteristics of the two groups were compared and presented in Table 2.0 and Table 3.0.As seen in Table 2.0 the baseline maternal variables viz., Anemia, Pregnancy Induced Hypertension (PIH), Gestational Diabetes Mellitus (GDM), Hypothyroid, Premature Rupture of Membranes (PROM), Antepartum Haemorrhage (APH), Amniotic Fluid Volume, Polycythemia and Type of delivery are comparable. The demographic variables, such as gestational age, birth weight and sex shown in Table 3.0 are similar in baseline characteristics. The observation of results for delivery room resuscitation and APGAR score also support this comparison.

Neonates with APGAR score less than 4 were not included in the study. In both the study groups the neonates with APGAR less than 7 were almost the same and were comparable.

Thus, from the tables 2.0 and 3.0, it is clearly illustrated that the baseline maternal and neonatal characteristics are similar between the two groups in the study and are comparable

The study was conducted after the approval from the Institution and getting the informed consent. The study period was from May 2021 to April 2022, in this study, 84 Very Low Birth Weight (VLBW) neonates (<1500 g) of <32 weeks of gestation were enrolled after the application of inclusion and exclusion criteria. The evaluation criteria for the study of the selected neonates were as follows: birth weight, gravida, anemia, PIH, GDM, hypothyroid, PROM, APH, amniotic fluid volume, antenatal steroids, steroids course completion, abnormal Doppler, type of delivery, required delivery room resuscitation, type of resuscitation, APGAR score, hypoglycemia, shock, sepsis, Downes score at admission, Downes score at 12 hours of admission, Downes score at 24 hours of admission, pulmonary congestion, feed intolerance, lft on day 1, lft on day 3, intraventricular haemorrhage, necrotising enterocolitis, bronchopulmonary dysplasia, retinopathy of prematurity, mechanical ventilation,

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requirement of CPAP, requirement of HFNC , duration of stay in level 3, length of hospital stay, weight gain.

The collected data was analyzed (after internal comparison, tabulation) and relevant inferences were made from descriptive and inferential statistics, on the grounds of the aims and objectives of the study.

Table 1: Non-inferiority - Two Groups - Parallel - Two proportions - Equal Allocation

Proportion in the intervention group	0.307
Proportion in the standard treatment group	0.147
Observed/Expected difference in proportions	-0.16
Non-inferiority margin	0.1
Power (1- beta) %	80
Alpha Error %	5
Required sample size in each group	42

Table 2: Comparison of baseline maternal variables between the study groups in the study population

Variables		Group A (n = 42)	Group B (n = 42)	P value
Anemia	Yes	32	31	0.801
	No	10	11	
PIH	Yes	15	18	0.503
	No	27	24	
GDM	Yes	4	1	0.360*
	No	38	41	
Hypothyroid	Yes	4	8	0.212
	No	38	34	
PROM	Yes	18	24	0.190
	No	24	18	
APH	Yes	4	3	1.000*
	No	38	39	
Amniotic Fluid Volume	Adequate	26	22	0.659
	Oligo	14	18	
Polycythemia	Abnormal Doppler			
	Yes	11	14	0.474
	No	31	28	
Type of delivery	NVD	17	19	0.659
	LSCS	25	23	

*Fisher exact test p value, rest are Chisquare test p values

Table 3: Comparison of baseline neonate variables

Variables		Group A (n = 42)	Group B (n = 42)	P-value
Gestational Age	<28 weeks	8	6	0.746
	28-32 weeks	19	18	
	32-34 weeks	15	18	
Birth weight	< 1 kg	9	9	0.970
	1 – 1.25 kg	18	19	
	1.25 – 1.5 kg	15	14	
Sex	Male	22	19	0.663
	Female	20	23	
Delivery Room Resuscitation	Yes	14	12	0.637
	No	28	30	
If Yes Type of Resuscitation	Tactile	2	3	0.434
	Bag and Mask	11	6	
	Intubation	1	3	
	NA	28	30	
APGAR Score	> 7 at 5 minutes	37	36	0.746
	< 7 at 5 minutes	5	6	

*Fisher exact test p value, rest are Chisquare test p values

Table 4: Comparison of outcome between the study populations in the study group (cumulative data)

Variables	Group A (n=42)	Group B (n=42)	P value
Mortality	3	6	0.483*
Shock	6	17	0.007
Sepsis	20	29	0.046
Hypoglycemia	7	7	1
Pulmonary congestion	17	24	0.034
Feed intolerance	9	16	0.095
Lft elevated on day 3	5	4	1.000*
Echo >1.5mm on day 1	5	11	0.095
Echo >1.5 mm on day 3	10	36	<0.001
Intraventricular hemorrhage	14	23	0.045
Necrotizing enterocolitis	6	7	0.763

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Bronchopulmonary dysplasia	6	8	0.558
Retinopathy of prematurity	10	20	0.038
Requiring mechanical ventilation	6	15	0.023
Requiring CPAP support	33	35	0.578
HFNC	38	36	0.5

*Fisher exact test p value, rest are Chisquare test p value

Table 5: Comparison of mortality between the groups in stratified birth weight category.

		Birth Weight					
		less than 1 kg		1 - 1.25 kg		1.25 -1.5kg	
		Group		Group		Group	
		A	B	A	B	A	B
Outcome	Mortality	2	1	1	4	0	1
	Discharge	7	8	17	15	15	13
	P value	1.000		0.340		0.483	

Table 6: Comparison of secondary outcome (perfusion abnormality) between the study groups in the study population (stratified)

		Birth Weight					
		< 1 kg		1 - 1.25 kg		1.25 -1.5kg	
		Group		Group		Group	
		A	B	A	B	A	B
Perfusion abnormality (shock)	Yes	3	3	1	11	2	3
	No	6	6	17	8	13	11
	P value	1.000		0.001		0.651	

Table 7: Comparison of secondary outcome (Downes score at 12 hours and 24 hours) between the study groups in the study population (stratified analysis)

		Birth Weight					
		< 1 kg		1 - 1.25 kg		1.25 -1.5kg	
		Group		Group		Group	
		A	B	A	B	A	B
Downes score at 12 hours	<4	3	2	10	1	4	4
	4-6	4	2	6	11	7	9
	>6	2	5	2	7	4	1
	P Value	0.341		0.003		0.365	
Downes score at 24 hours	<4	6	3	15	1	9	7
	4-6	3	2	3	11	5	6
	>6	0	4	0	2	1	1
	P value	0.074		<0.001		0.858	

Table 8: Comparison of sepsis between the study groups in the study population (stratified analysis)

		Birth Weight					
		less than 1 kg		1 - 1.25 kg		1.25 -1.5kg	
		Group		Group		Group	
		A	B	A	B	A	B
Sepsis	Yes	7	4	8	14	5	11
	No	2	5	10	5	10	3
	P VALUE	0.335		0.099		0.025	

Table 9: Comparison of incidence of pulmonary congestion between the study groups in the study population (stratified analysis)

		Birth Weight					
		Less than 1 kg		1 - 1.25 kg		1.25 -1.5kg	
		Group		Group		Group	
		A	B	A	B	A	B
Pulmonary Congestion	Yes	6	7	5	12	6	10
	No	3	2	13	7	9	4
	P Value	1.000		0.007		0.139	

Table 10: Comparison of feed intolerance between the study groups in the study population (stratified analysis)

Variables	Covariates	Group A (n = 42)	Group B (n = 42)	P value
Secondary outcome: Feed Intolerance	< 1 kg	1	4	0.163
	1 – 1.25 kg	3	9	
	1.25 – 1. 5 kg	5	3	

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Table 11: Comparison of duct diameter seen by echo on day 3 of life between the study groups in the study population.

		Birth Weight					
		less than 1 kg		1 - 1.25 kg		1.25 -1.5kg	
		Group		Group		Group	
		A	B	A	B	A	B
ECHO on Day 3 >1.5 mm	Yes	2	9	5	16	3	11
	No	7	0	13	3	12	3
	P value	0.002		0.001		0.003	

Table 12: Comparison of intraventricular hemorrhage between the study groups in the study population (stratified)

		Birth Weight					
		Less than 1 kg		1 - 1.25 kg		1.25 -1.5kg	
		Group		Group		Group	
		A	B	A	B	A	B
IVH	Yes	5	5	6	15	3	9
	No	4	4	12	4	12	5
	P Value	1.000		0.008		0.025	

Table 13: Comparison of incidence of necrotizing enterocolitis between the study groups in the study population (stratified)

Variables	Covariates	Group A (n = 42)	Group B (n = 42)	P value
NEC	< 1 kg	1	2	0.879
	1 – 1.25 kg	4	4	
	1.25 – 1. 5 kg	1	1	

Table 14: Comparison of incidence of bronchopulmonary dysplasia between the study groups in the study population (stratified)

Variables	Covariates	Group A (n = 42)	Group B (n = 42)	P value
BPD	< 1 kg	3	3	0.646
	1 – 1.25 kg	3	4	
	1.25 – 1. 5 kg	0	1	

Table 15: Comparison of retinopathy of prematurity between the study groups in the study population (stratified)

		Birth Weight					
		Less than 1 kg		1 - 1.25 kg		1.25 -1.5kg	
		Group		Group		Group	
		A	B	A	B	A	B
Retinopathy of Prematurity (ROP)	Yes	6	8	3	12	1	8
	No	3	1	15	7	14	6
	P value	0.576		0.007		0.005	

Table 16: Comparison of duration and requirement of mechanical ventilator support between the study groups in the study population (stratified)

		Birth Weight					
		Less than 1 kg		1 - 1.25 kg		1.25 -1.5kg	
		Group		Group		Group	
		A	B	A	B	A	B
	Yes	3	3	2	9	1	3
	No	6	6	16	10	14	11
Mechanical Ventilation	P value	1.000		0.029		0.330	

Table 17: Comparison of duration and requirement of CPAP support between the study groups in the study population (stratified)

Variables	Covariates	Group A (n = 42)	Group B (n = 42)	P value
CPAP Support	< 1 kg	9	9	0.817
	1 – 1.25 kg	15	14	
	1.25 – 1. 5 kg	9	12	

Table 18: Comparison of liver function tests on day 3 of life between the study groups in the study population (stratified)

Variables	Covariates	Group A (n = 42)	Group B (n = 42)	P value
Secondary outcome:				
LFT on day 3 elevated	< 1 kg	3	1	0.196
	1 – 1.25 kg	1	2	
	1.25 – 1. 5 kg	1	1	

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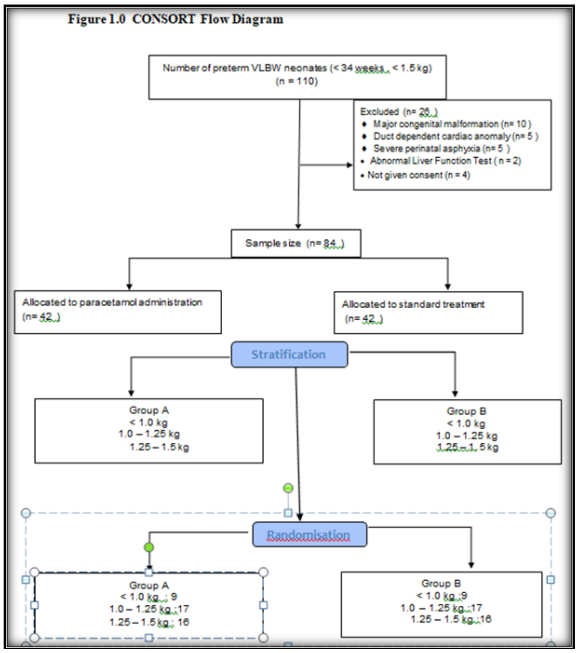
Table 19: Comparison of Birth weight with median duration stay in level 3 stay for Group A and Group B-Unpaired t test / ANOVA test

	Level 3 stay	GROUP A		GROUP B		Unpaired t test P value
		Mean	SD	Mean	SD	
Birth Weight	< 1 kg	32.4	9.8	33.0	10.2	0.914
	1 - 1.25 kg	15.8	8.7	25.3	13.0	0.019
	1.25 -1.5 kg	13.4	9.9	15.4	8.1	0.569
	ANOVA test p value	<0.001		0.003		

Table 20: Comparison of the median duration of hospital stay between both the groups in association with birth weight using Mann Whitney U test.

	Length of hospital stay	GROUP A			GROUP B			Mann Whitney U test
		Median	Q1	Q3	Median	Q1	Q3	p value
Birth Weight	< 1 kg	64.0	47.0	65.0	70.0	54.0	75.5	0.536
	1 - 1.25kg	35.0	25.0	45.0	35.0	25.0	45.0	0.882
	1.25 -1.5kg	25.0	18.0	45.0	22.0	18.0	30.0	0.555

Relevant statistical tests for comparing the study population were made. Categorical variables were presented as frequency and percentages and continuous variables as Mean / Median ± Standard deviation. Association between categorical variables was examined using Chi square / Fischer exact. The association of continuous variables between both groups was measured by T-test / Mann Whitney U test/ Kruskal Wallis test. Inferences were drawn for P values with <0.05 as statistically significant. SPSS Package 16.0 and Microsoft Excel 2010 were used for the analysis of the data. The results are presented in table 4.0 and the inferences drawn are discussed. As illustrated from Table 4.0 , it is evident that there is no change in rate of mortality between the intervention and control group .However the incidence of other parameters like shock, sepsis, pulmonary congestion, diameter of ductus arteriosus on day 3, intra-ventricular hemorrhage, retinopathy of prematurity and requirement of mechanical ventilation showed significant variation between the intervention and control groups with a reduced incidence observed in the intervention group. Hence, it is inferred that administration of prophylactic paracetamol maybe beneficial in reducing the comorbid factors which may influence the overall outcome of preterm babies.



DISCUSSION

Hemodynamically significant PDA has a major influence on the immature babies in terms of occurrence of respiratory distress syndrome, necrotising enterocolitis etc., Hence closure of the ductus and more specifically timing of closure is crucial.

Till date, several RCTs and observational studies for the treatment of HsPDA in preterm neonates have been conducted. In our study, a total of 84 neonates were included after getting written informed consent and were stratified into 3 categories based on birth weight. The statistical analysis was also done in a way that it included the analysis of both cumulative data and stratified data according to birth weight.

There was no decrease in mortality rate in neonates who received prophylactic paracetamol implicating that even though paracetamol helps in closure of hsPDA with very minimal side effects, many other factors like prematurity, birth weight, antenatal risks also come into play and the mortality rate couldn't be

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reduced with the administration of paracetamol alone.

Nonetheless, paracetamol by effectively closing the duct helps in reducing the incidence of other comorbidities as explained in [Table 4] and discussed below.

Ductus was observed to be hemodynamically significant in 23 % of neonates who received prophylactic paracetamol compared to the control group wherein 80% had a patent ductus on day 3 of life necessitating treatment. This is consistent with the findings of a study conducted by Al - Lawama et al,[27] at Jordan's University on preterm neonates aged 32 weeks. Also, further analysis after stratification showed an effective duct closure in neonates belonging to all birth weight categories (<1kg,1-1.25 kg ,1.25-1,5 kg) with a p value of 0.002, 0.001 and 0.003 respectively.

The study by Sunil et al,[28] at the Kempagowda Institute of Medical Sciences in Bangalore showed PDA closure with paracetamol had no significant side effects in 27 out of 36 babies (75%). A study conducted at Manipal Hospital in Bangalore by Mohanty et al,[29] in preterm neonates 32 weeks reported a closure rate of 72.5% with no major complications.

Dang et al,[30] studied 160 infants with gestational age 34 weeks who were given 15mg/kg paracetamol every 6 hours for three days and discovered that the ductus was closed in 81.2% of the paracetamol group and 78.8% of the ibuprofen group.

In the EPAR trial, it is concluded that early administration of paracetamol reduced the number of infants requiring intervention for PDA. Short- term safety data were reassuring, acknowledging the small number of infants involved in the study.

Hence, all the mentioned studies conducted till date show that paracetamol is effective in closure of PDA and also the early administration is efficacious as shown in EPAR trial which is consistent with the undertaken study. But, studies on the after effects of ductal closure like mortality and other comorbities are very minimal and yet to be studied extensively, which is undertaken in this study.

In this study the secondary outcomes are analysed on a cumulative scale and after stratification to think through if birth weight has any role to play.

On cumulative data analysis of other secondary outcomes, there is a noteworthy change in the incidence of perfusion abnormality (p value 0.007), sepsis (0.046), pulmonary congestion (p value 0.034), intra-ventricular haemorrhage (p value 0.045), retinopathy of prematurity (p value 0.038) and requirement of mechanical ventilation (0.023).

On stratified analysis, a significant change was noted especially in neonates belonging to 1-1.25 kg birth weight. The incidence of perfusion abnormality (p value 0.0.001) [Table 6], downes score at 12 hours (p value 0.003)and 24 hours (0.006) [Table 7], pulmonary congestion (p value 0.007) [Table 9], intra-ventricular haemorrhage (p value 0.008) (table 12.0), retinopathy of prematurity (p value 0.007) [Table 15] and requirement of mechanical ventilation (0.029) [Table 16] were lower compared to the < 1kg and 1.25-1.5 kg category neonates. Also the median duration of stay in level 3 [Table 19] which was not influenced in the overall comparison was also less in neonates of 1-1.25 kg birth weight.

Hence, even though ductal closure was seen in neonates of all birth weight categories, the neonates with a birth weight of 1-1.25 kg had a better course and outcome. Though the neonates < 1 kg survive, they succumb to many comorbidities due to their immaturity and premature arrest in development of organ systems which couldn't be overcome with early ductal closure alone. Many other extravagant support systems and care is also required to avoid the stormy course experienced by these extreme low birth weight neonates.

On studying the other group (1.25 – 1.5 kg), there was not much change except for a few parameters like sepsis [Table 8], intra-ventricular haemorrhage [Table 12] and retinopathy of prematurity [Table 15].

Regarding the adverse effects following paracetamol, only a few had elevated liver parameters which did not have much implication on their clinical course. This is in accordance with studies conducted by Oncel et al, Al- Lawama et al, Sinha et al, Terrin et al, Dang et al.[26-31]

CONCLUSION

Paracetamol is efficacious in closure of PDA and is usually administered once signs and symptoms of hemodynamically instability occur due to PDA and pulmonary shunting of blood. When given prophylactically within 24 hours of life, paracetamol by closing the patent ductus may help the neonates in overcoming the drastic course and survive the dreadful complications that may follow. In this randomised control trial, a comparison was made between early and routine paracetamol administration and the projected results convey a beneficial role of paracetamol in reducing the co morbidities in the preterm immature neonates and improve their clinical outcome. Moreover, early closure of the ductus has been observed to be more effective in the neonates of 1-.1.25 kg category. These findings tentatively conclude that prophylactic paracetamol by inducing early closure improves the outcome in preterm very low birth weight neonates. However, more studies with larger sample size and long term follow up are essential to support the evidence.

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