ORIGINAL RESEARCH PAPER

Neonatology

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EFFICACY AND SAFETY OF ORAL IBUPROFEN IN PDA CLOSURE IN PRETERM NEONATES

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ABSTRACT

Objective: To study the efficacy and safety of oral ibuprofen therapy in PDA closure in preterm babies

Methods: 48 preterm neonates with symptomatic PDA, confirmed by Echocardiography within 48-96 hours after birth, were included in this prospective analytical study. Symptomatic PDA means any of the following-

1. Murmur
2. Minimum 3 among-
a. Tachycardia(>170/min)
b. Bounding pulses
c. Hyperdynamic apex
d. Tachypnea>70/min
e. Features of cardiac failure
3. Cardiomegaly on chest X-ray
4. Echocardiographic evidence-ductal diameter>1.4mm, LA/AO ratio>1.3 with respiratory distress

Blood investigations and neurosonogram were taken for all infants before and after brufen therapy.Oral ibuprofen suspension 10mg/kg was given on the first day and 5 mg/kg each 24 hours apart. All neonates were monitored for oliguria, bleeding diathesis, bloody gastric aspirate, pulmonary hemorrhage, intraventricular hemorrhage(IVH) and feed intolerance. Repeat echo was done 24 hours after the last dose of ibuprofen.

Results: PDA closure was achieved in 43 out of 48 neonates(89.6%), while 5 required surgical closure, Among the 43 in whom PDA closed, 6 required repeat ibuprofen therapy. Complications included pulmonary hemorrhage in 2(4.2%), thrombocytopenia in 6(12.5%), bleeding tendency in 5(10.4%), bloody gastric aspirate in 5(10.4%), IVH in 2(4.2%), feed intolerance in 4(8.3%) and oliguria in 3(6.2%).However no statistically significant difference regarding complications was observed between those who had successful closure of PDA and those who required surgery. Regarding survival, 1 baby died due to sepsis on day 15 of life, but after successful closure of PDA.

Conclusion: Oral Ibuprofen was found to be safe and efficacious in closing PDA in preterm neonates.

INTRODUCTION:

Symptomatic patent ductus arteriosus (PDA) is a common problem in preterm neonates, especially in babies with respiratory distress syndrome (RDS). Substantial blood shunting from left side of the heart to right side through the ductus raises the chances of IVH, reduces mesenteric blood flow resulting in NEC, bronchopulmonary dysplasia and death.[1] Cotton et al[2] estimated that 44% of infants with birth weight <1.5Kg develop respiratory distress and cardiac failure due to Patent ductus arteriosus. Initially, this stimulated surgical intervention by Kitterman et al in 1972. After the successful results from experimental studies with intravenous indomethacin on infant lambs by Heymann study[3]and in human infants by Friedman et al [4]treatment with medications was tried. Early studies assessed about the need of ventilatory support, incidence of pneumothorax and chronic lung disease and mortality. Initially, intravenous indomethacin was commonly accepted as the conventional pharmacologic treatment for closing ductus. But there is a fear about the safety of indomethacin, since it affects blood flow to all the organs like kidney, gastrointestinal tract[5] and brain [6] and may lead to complications such as renal dysfunction,Necrotizing enterocolitis, intestinal bleed and cerebral hypoxia.

Nowadays Ibuprofen was found to close PDA effectively in animals without affecting the blood flow to brain,intestines and kidneys[7]. It has been proved that ibuprofen closes the ductus without the complications of reduced mesenteric, renal, or cerebral blood flow[8]. A recent Cochrane review[9] concluded that there is no significant difference in the effectiveness of intravenous ibuprofen as compared to intravenous indomethacin in achieving ductal closure, while ibuprofen reduces the risk of oliguria, it does not appear to confer any additional benefits over indomethacin for the treatment of PDA. Subsequently several oral ibuprofen pilot studies[9] have shown equal efficacy (95%), and ease of administration. There are no Indian studies in the literature reporting the usefulness of oral ibuprofen. This study was therefore undertaken to assess the safety and efficacy of oral ibuprofen in preterm neonates with PDA.

AIM AND OBJECTIVE:

The main aim of our study is to analyse and prove whether oral ibuprofen therapy is effective in closure of significant PDA in preterm babies and about the side effects of the drug were analysed.

STUDY DESIGN:

Prospective analytical study

STUDY POPULATION:

Babies admitted in NICU (neonatal intensive care unit), Institute of Social Paediatrics,Government Stanley Medical College, Chennai.

STUDY PERIOD:

November 2014 – October 2016.

SAMPLE SIZE:

48 preterm neonates.

INCLUSION CRITERIA:

Preterm neonates gestational age <37 weeks with symptomatic PDA confirmed by echocardiography within 48-96 hours after birth were included in the study.

EXCLUSION CRITERIA:

Preterm babies with

-Other major congenital anomalies,
- Complex heart disease
- Thrombocytopenia
- Recent intra ventricular haemorrhage (within in 24 hrs)

- Serum creatinine levels >1.6 mg/dl
- Blood urea nitrogen concentration more than 40 mg/ dl
- Hyperbilirubinemia necessitating exchange transfusion
- Extreme low birth weight babies who are very sick.
- DIC

METHODOLOGY:

Preterm infants fulfilling the inclusion criteria are selected (including ECHO)

- Baseline blood investigations to evaluate about the safety later.
- Oral ibuprofen therapy was started as soon as a significant PDA was detected and diagnosis confirmed.
- These babies were given oral ibuprofen suspension 10 mg/kg/body weight as the first dose, through NG tube followed at 24-hourintervals by 2 additional doses of 5 mg/kg each
- All babies getting Ibuprofen had a
- complete blood count
- platelet count
- blood urea, creatinine
- urinary output monitoring
- X-ray chest

Neurosonogram (to evaluate intra ventricular haemorrhage later) were done before and after ibuprofen therapy.

- Serum electrolytes and serum bilirubin were done if needed.
- All neonates were monitored for the presence of
  - Oliguria
  - Bleeding diathesis
  - Raised BUN
  - Serum creatinine
  - Decreased platelets and other bleeding manifestations
  - Bloody gastric aspirate
  - Pulmonary haemorrage,
  - IVH and feed intolerance
- All babies underwent repeat echo-cardiography 24 hrs after the last dose to confirm closure of PDA .
- Assessed for need of repeat ibuprofen or surgical closure.

STATISTICAL ANALYSIS:

The information collected regarding all the selected cases were recorded in a Master Chart.

Data analysis was done with the help of computer using Epidemiological Information Package (EPI 2010) developed by Centre for Disease Control, Atlanta.Using this software range, frequencies, percentages, means, standard deviations, chi square and 'p' values were calculated.

Kruskal Wallis chi-square test was used to test the significance of difference between quantitative variables and Yate's chi square test for qualitative variables.A 'p' value less than 0.05 is taken to denote significant relationship.

RESULTS AND OUTCOME:

Out of 48 cases,PDA closed in 92% of male babies and 87% of female babies. Even though PDA closed better in male babies in our study, gender doesn't have any statistical significance with ductal closure**(p value-0.45)**.4 out of 5 babies in whom PDA was not closed had a birth weight lesser than 1.5 kg**(p value-0.08)**. But this was not statistically significant.4 out of 5 babies who failed PDA closure(with ibuprofen therapy)were born before 32 weeks which was not of any significance**(p value-0.58).**The average duration of stay was longer in oral ibuprofen failure group(20 days) compared to the ones who responded to treatment(13 days). This hospital stay may vary because of associated preterm complications and not purely due to PDA but this was statistically significant **(p value-0.0001).** Out of 5 babies who failed closure, 4 had bounding pulses**.** So there is less likely chance of closure with oral ibuprofen with such clinical signs **(p value=0.0366).** PDA closure was affected by the requirement of inotropic support but was relatively unaffected with the need for ventilator or surfactant. 5/48 babies in whom PDA was not closed ,3 babies (60%) required inotropic support. Thus PDA closes to a lesser incidence in babies requiring inotropic support. **(p value-0.0054)** All the 4 babies with the ductal diameter more than 3 mm fail to close even with repeat oral ibuprofen therapy. These babies required surgical ligation. As per our study, Ductal diameter has statistically significant predictability in ductal closure or requiring other modalities of treatment**.(p value = 0.0035)** 5 babies with failed PDA closure had LA/AO ratio more than 1.55. The mean LA/AO ratio for babies in whom PDA was closed was 1.55 whereas in non-closed individuals, it was 1.59 but this was not of any significance. There are no statistically significant difference in occurrence of these complications among preterm babies who had successful closure and those babies who required surgery.

TABLE 1 :BASELINE CHARACTERISTICS

a)BIRTH WEIGHT1.	66 ± 0.39kg(range 1.1-2.5kg)
<1500	23(47.9%)
1501-2000	15(20.3%)
2000-2500	10(30.8%)
b)GESTATIONAL AGE	32.3±1.7weeks(range 28-34 wks)
<28 weeks	2(4.2%)
28-32 weeks	28(58.3%)
c)GENDER	
Male babies	25(52.1%)
Female babies	23(47.9%)
d)DURATION OF HOSPITAL STAY	
	13.8± 4.3 days (range 10-28 days)
<10 days	7(14.6%)
11-15 days	29(60.5%)
15-20 DAYS	8(16.6%)
>20 DAYS	4(8.3%)

TABLE 2: MURMUR

Murmur	Cases	
	No	%
Systolic	44	91.7
Continuous	4	8.3

TABLE 3: SUPPORTIVE TREATMENT GIVEN

Surfactant treatment(n):	
• Given	2(4.2%)
• Not given	46(95.8%)
Inotropic support(n):	
• Given	5(10.4%)
• Not Given	43(89.6%)
Mechanical Ventilation (n):	
• Done	2(4.2%)
• Not done	46(95.8%)

TABLE 4: CLOSURE OF PDA

Successful closure with oral ibuprofen (n)	37(77.1%)
Successful closure with repeat ibuprofen (n)	6(12.5%)
Surgery	5(10.4%)

TABLE 5:COMPARITIVE ANALYSIS

	CLOSED GROUP n=43 MEAN AND S.D.	NON CLOSED GROUP n=5 MEAN AND S.D.	p VALUE
GESTATIONAL AGE (WEEKS)	32.3 (1.7)	32 (1.4)	0.5874
BIRTH WEIGHT(Kg)	1.69 (0.4)	1.39 (0.24)	0.0899
DAY OF STARTING ORAL IBUPROFEN(DAYS)	1.59(2.44)	2.00(1.65)	0.576
DURATION OF STAY(DAYS)	13(3.4)	20.8(5.4)	0.0001
DUCTAL SIZE (mm)	2.09(0.39)	3.04(0.6)	0.0035
La/Ao RATIO	1.55(0.11)	1.59(0.06)	0.2647

	CLOSED GROUP No. AND %	NOT CLOSED GROUP No. AND %	p VALUE
BOUNDING PULSES	12(75%)	4(25%)	0.0366

MURMUR -SYSTOLIC-44 -CONTINUOUS-4	41(93.2%) 2(50%)	3(6.8%) 2(50%)	0.064
SURFACTANT GIVEN	2(100%)		0.8009
INOTROPIC SUPPORT	2(40%)	3(60%)	0.0054
PULMONARY HAEMORRHAGE	2(100%)		0.8009
BLOODY GASTRIC ASPIRATE	3(75%)	1(25%)	0.3658
OLIGURIA -YES(3) -NO(45)	 2(66.7%) 41(91.1%)	 1(33.3%) 4(8.9%)	0.2885
RAISED BUN AND CREATININE -YES(2) -NO(46)	 2(100%) 41(89.1%)	 5(10.9%)	0.8009
DECREASED PLATELETS -YES(6) -NO(42)	 5(83.3%) 38(90.5%)	 1(16.7%) 4(9.5%)	0.5032
BLEEDING TENDENCY -YES(5) -NO(43)	 4(80%) 39(90.7%)	 1(20%) 4(9.3%)	0.4378
IVH -YES(2) -NO(46)	 2(100%) 41(89.1%)	 5(10.9%)	0.8009

CONCLUSION:

As per our study, Oral ibuprofen was found to be safe and efficacious in closing PDA in preterm neonates.

LIMITATIONS:

This is not a comparative study with other drugs,study population is very small,Extreme low birth weight infants are not included in the study due to practical problems, associated major complications,Intravenous ibuprofen has 100% bioavailability. But the bioavailability of the oral ibuprofen administered in our study was not measured.

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