

Restrictive Threshold for the Management of Patent Ductus Arteriosus in Very Low Birth Weight Neonates

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Objectives: To compare outcomes of very low birth weight (VLBW) neonates before and after the change in practice for treatment of PDA. **Methods:** Medical records of VLBW neonates were reviewed. Neonates were categorized in two groups: Period I (January, 2012 to July, 2015) and Period II (August, 2015 to December, 2016). The primary outcome of study was composite outcome of death or broncho-pulmonary dysplasia (BPD). **Results:** The composite outcome (Death/BPD) was comparable in two groups; adjusted OR (95% CI) 1.1 (0.6, 1.9). Mortality and severe BPD were also comparable. The pharmacological treatment for PDA was required in 8.4% vs 2.6% of VLBW neonates during Period I and II, respectively ($P=0.03$). Durations of invasive and noninvasive ventilation were comparable during two periods. **Conclusion:** Restrictive threshold for management of PDA in VLBW neonates may not be associated with increase in morbidities or mortality and possibly would reduce need for pharmacological treatment or surgical ligation.

Keywords: Indomethacin, Paracetamol, Ligation, Outcome.

A hemodynamically significant patent ductus arteriosus (PDA) in preterm neonates is considered a risk factor for mortality, and morbidities such as bronchopulmonary dysplasia (BPD), necrotizing enterocolitis (NEC), and intraventricular hemorrhage (IVH) [1]. A causal relationship between PDA and these adverse outcomes; however, has not been established [2,3]. Traditionally, therapeutic closure of hemodynamically significant PDA (hsPDA) in preterm neonates is considered based on certain clinical and echocardiographic criteria [4]. However, there is no unanimity regarding definition of hsPDA and guidelines for its management. Systematic reviews have not observed a significant reduction in respiratory morbidities or mortality with early inter-vention [5]. Moreover, both pharmacological treatment or surgical ligation for PDA could be associated with adverse effects on multiple organ systems [6,7].

Recent observational studies suggest that PDA closes spontaneously in most preterm neonates, and use of a conservative approach for its management does not result in an increase in morbidity or mortality [8-10]. With this background, we changed our unit practice in July, 2015, and adopted more restrictive guidelines for therapeutic closure for PDA in preterm neonates. We planned this study with an objective to compare outcomes of very low birth weight (VLBW) neonates before and after the change

in practice for treatment of PDA.

METHODS

Medical records of all VLBW neonates admitted to neonatal intensive care unit, Sir Ganga Ram Hospital, New Delhi, between January 2012 and December 2016 were reviewed after approval by institutional ethics committee. Neonates admitted beyond 72 hours of age or those with major congenital malformations were excluded. Baseline characteristics of enrolled neonates were recorded in a predesigned proforma. Based on date of admission, neonates were categorized in two groups: Period I (January, 2012 to July, 2015) and Period II (August, 2015 to December, 2016). The primary outcome of this study was composite outcome of death or BPD. The secondary outcome measures were need for pharmacological or surgical treatment for PDA, duration of ventilation, and need for postnatal steroids and diuretics.

During both periods, evaluation for PDA was considered, if a neonate required invasive ventilatory support with $\text{FiO}_2 > 0.3$ and/or mean airway pressure (MAP) $> 8 \text{ cm H}_2\text{O}$ beyond 48-72 hours of life or had other clinical features suggestive of hsPDA. All echocardiograms were performed by pediatric cardiologists. During Period I, PDA was considered hemodynamically significant and therapeutic closure of

PDA was attempted, if duct size was >1.5 mm and left atrium to aortic root ratio (LA: Ao ratio) was >1.5 . During Period II, PDA was considered hemodynamically significant, if echocardiographic assessment revealed an unrestrictive duct (laminar flow with peak velocity <1.5 m/sec) and LA: Ao ratio >2 . During both periods, oral ibuprofen was used as first line medication. If pharmacological treatment was unsuccessful after two courses or was contraindicated, surgical ligation of PDA was considered.

The overall management of VLBW neonates was similar during both the study periods. Fluid intakes were adjusted as per daily weight pattern, allowing 1-2% physiological weight loss per day during the first week of life. Cumulative days on respiratory support and supplemental oxygen were noted, BPD was defined as per NIH consensus definition 2001 [11].

Statistical analyses: Statistical analysis was done using SPSS version, 17.0. Statistical differences between two study periods were computed with chi square test for categorical variables and Student *t* test or Mann-Whitney U test as applicable for quantitative variables. Logistic regression analysis was applied to adjust for possible confounders among demographic and perinatal characteristics. *P* value <0.05 was considered statistically significant.

RESULTS

Of 528 VLBW neonates admitted during the study period, 509 were enrolled and analyzed; 394 in Period I and 115 in Period II. Remaining neonates were excluded from analysis; 17 were admitted 72 hrs after birth and 2 were shifted to another NICU during first week of life. Baseline characteristics of study groups are depicted in **Table I**.

The mortality and composite outcome of death/BPD were comparable during the two periods (**Table II**). On univariate analysis, BPD rate was higher during Period II. After adjustment for potential confounders (gestation <28 weeks, antenatal steroid, surfactant administration and culture positive sepsis), all outcomes were comparable. The pharmacological treatment for PDA was required in 8.4% vs 2.6% of VLBW neonates during Period I and II, respectively ($P=0.03$). Two (0.5%) neonates in Period I and none in Period II required surgical ligation for PDA. Among neonates requiring ventilatory support, durations of invasive and noninvasive ventilation were comparable during the two periods (**Table II**).

DISCUSSION

There is a wide variation in thresholds for PDA treatment across different NICUs with available options of

prophylactic closure, early targeted treatment or a conservative approach where intervention is delayed beyond 1st week [12-14]. We changed our unit practice for therapeutic closure of PDA in July, 2015 to a more conservative approach. We observed a high spontaneous closure rate during period II, only 3 (2.6%) neonates received treatment for PDA and all were below 28 weeks of gestation. These findings are consistent with recent reports of high spontaneous closure rates with a more conservative approach for PDA [8-10].

Respiratory morbidity among preterm neonates with PDA is a major concern, prompting neonatologists to attempt early therapeutic closure of ductus. We found that all grades of BPD, death and combined death/BPD were comparable during the two periods. Our observations are similar to recent reports, where, a conservative approach towards PDA was associated with spontaneous closure of PDA in most neonates without increase in morbidities or mortality [8-10]. In fact, Sung, *et al.* in a before-after study reported a lower BPD rates among neonates with gestation of 23-26 week, with a non-intervention approach compared with a mandatory closure of PDA [15]. The authors observed that with non-intervention and restrictive fluid intakes, 95% PDA closed spontaneously by discharge from NICU; only 3 neonates required transcatheter occlusion later during infancy. These observations of high spontaneous PDA closure rate with a conservative approach without an increase in neonatal morbidities and mortality are reassuring and warrant

Table I Characteristics of VLBW Neonates (N=509)

Characteristics	Period 1 (n=394)	Period 2 (n=115)
Birthweight, g ^a	1112 (254)	1130 (269)
Gestational age, wk ^a	29.9 (2.6)	29.6 (2.6)
Gestation <28 wk ^b	68 (17.2)	30 (26.0)
Small for gestation	126 (31.9)	42 (36.5)
Antenatal steroids ^b	309 (78.4)	79 (68.6)
Complete course	239 (60.6)	65 (56.5)
UA Doppler flow		
Reduced	72 (18.2)	13 (11.3)
Absent/reversed	65 (16.4)	20 (17.4)
Need for respiratory support		
Non-invasive	103 (26.1)	41 (35.6)
Invasive	147 (37.3)	51 (44.3)
Surfactant use ^b	122 (31)	50 (43.4)
Caffeine usage	230 (58.4)	62 (53.9)
Culture positive sepsis ^b	94 (23.9)	38 (33)

ANS- antenatal steroid; UA- umbilical artery. Data expressed as n (%), or ^amean (SD); $P > 0.05$ for all comparisons except ^b $P < 0.05$.

WHAT THIS STUDY ADDS?

- Restrictive threshold for management of PDA in VLBW neonates may not be associated with an increase in morbidities or mortality and possibly would reduce pharmacological treatment.

Table II Outcomes of VLBW Neonates During Two Study Periods

Outcome	Period I (n=394)	Period II (n=115)	Period I vs II
Death/BPD ^b	106 (26.9)	38 (33)	1.1 (0.6, 1.9)
Death ^b	80 (20.3)	24 (20.9)	1.1 (0.63, 2.0)
BPD ^b	31 (7.9)	17 (14.8)	1.7 (0.83, 3.5)
Severe BPD ^b	9 (2.3)	2 (1.7)	2.3 (0.4, 12.8)
Pharmacological treatment	33 (8.4)	3 (2.6)	0.03
Age at medication, d ^{a,c}	4 (3, 7.5)	6 (4, 14)	0.81
Duration of ventilation, d ^{a,c}			
Invasive	1 (3, 7)	3 (1, 15)	0.22
Non-invasive	4 (1, 10)	4 (1, 15)	0.69
Duration of hospitalization, d ^{a,c}	29 (14, 44)	28 (15, 56)	0.32
Postnatal steroid use ^c	10 (2.5)	6 (5.2)	0.21
Intraventricular hemorrhage ^c			
Any grade	19 (4.8)	5 (4.3)	1.0
Grade III/IV	6 (1.5)	3 (2.6)	0.42
NEC stage >2 ^c	11 (2.8)	3 (2.6)	1.0

Data expressed as n (%) or ^amedian (IQR); BPD; bronchopulmonary dysplasia; comparison between two study periods in ^badjusted OR (95% CI) or ^cP value. 2 children each in period I underwent surgical ligation or had diuretic use as compared to none in period II.

revisiting conventional liberal treatment practices. In the absence of proven therapeutic benefits of the traditional approaches, there is a need to devise more restrictive guidelines for the management of PDA that would limit exposure to possible harmful effects of medical or surgical treatment in these tiny neonates.

The limitations of our study include the single center, non-randomized study design, and few extremely preterm neonates <27 weeks in this cohort, making our findings less generalizable for this subset. Further, in before-after study, impact of changes in NICU practices over the year and improvement in overall care cannot be denied.

In conclusion, restrictive threshold for management of PDA in VLBW neonates may not be associated with increase in morbidity or mortality, and possibly would reduce need for pharmacological treatment or surgical ligation. There is need for adequately powered rando-

mized controlled trials to evaluate impact of restrictive approach for the management of PDA on both short-term and long-term outcomes.

Ethical clearance: Institutional ethics committee, Ganga Ram Hospital; No. EC/11/171285, dated 31 March, 2018.

Contribution: MM, SS: planned the study; MM, AT: collected data; MM, SS: analyzed the data; MM, SS, AT: wrote the manuscript. AS edited the manuscript.

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