

Resistive Indices of Cerebral Arteries in Preterm Infants of Less Than 32 Weeks of Gestational Age during Stay in NICU and Impact of PDA

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Abstract

Background: Cerebral vascular anatomy and disturbance of cerebral hemodynamics are key factors in pathophysiology of brain injury in preterm infants. There is renewed interest in non- invasive methods to evaluate cerebral blood flow. One such method assessing one aspect of cerebral blood flow is measuring the resistive index in cerebral arteries using colour doppler imaging. The purpose of the study is to evaluate RI values of cerebral arteries in a prospective cohort of preterm infants less than 32 weeks of gestational age during stay in NICU and to compare RI values of cerebral arteries between neonates with hemodynamically significant PDA and those without PDA.

Results: We examined 70 infants. We found that the resistive indices values differed among the arteries. The RI values were calculated and then compared between hemodynamically significant PDA cases and hemodynamically insignificant PDA/non-PDA cases. Vessels with larger diameters showed significantly higher resistive indices. Resistive index in infants

without patent ductus arteriosus was lower than that in infants with hemodynamically significant PDA (mean in Right ICA: 0.76 and 0.85 respectively; $p < 0.001$), mean in Left ICA: 0.77 and 0.86 respectively; $p < 0.001$), mean in Anterior cerebral artery: 0.74 and 0.84 respectively; $p < 0.001$) and mean in Basilar artery 0.71 and 0.82 respectively; $p < 0.001$).

Conclusion: The resistive indices differed depending on the artery examined. Preterm infants without patent ductus arteriosus had a slightly lower resistive index in intracerebral arteries than infants with hemodynamically significant patent ductus arteriosus. The potential implications of this study by measuring RI values in PDA patients, we can predict the future risk related to cerebral vascular damage in pre-term infants, so knowing the ri values we can intervene early.

Keywords : Resistive index, Transthoracic echocardiography, Hemodynamically significant patent ductus arteriosus, Hemodynamically insignificant patent ductus arteriosus.

Introduction

Preterm birth is defined as any birth before 37 weeks completed weeks of gestation.⁽¹⁾ arterial hemodynamics in the cerebral circulation are affected by normal maturational events in the healthy new-born. The resistive index in the anterior cerebral artery decreases in preterm infants.^(2,3) this trend is associated with increasing diastolic flow velocities and may be related to weighing over 2500gm at birth, although the range of normal values is broad, no great variability should be seen in the individual patient. Cerebral vascular anatomy and disturbance of cerebral hemodynamics are key factors in pathophysiology of brain injury in preterm infants^[4]. Therapeutic options for brain injury in these infants are currently lacking, so clinicians focus on prevention through hemodynamic monitoring. Therefore, there is renewed interest in non-invasive methods to evaluate cerebral blood flow. One such method assessing one aspect of cerebral blood flow is measuring the resistive index in cerebral arteries using colour Doppler imaging. The internal carotid artery, basilar artery, anterior cerebral artery and lenticulostriate arteries can be easily visualized with colour doppler imaging [5]. Flow can be evaluated and peak systolic velocity, end-diastolic velocity and resistive index can thus be obtained. Resistive index is defined as (peak systolic velocity – end-diastolic velocity) /peak systolic velocity^[6]. Low resistive index is considered a possible sign of luxury perfusion in term birth asphyxia^[7,8,9,10].The aim of this prospective observational study was to compare the cerebral autoregulatory capacity of preterm VLBW infants. A patent ductus arteriosus is considered to be the usual cause for elevated resistive index in preterm infants^[8-13]The cerebral circulation has a low vascular resistance which ensures the brain of continuous advancing blood flow throughout the cardiac cycle. The

PI value denotes the degree of resistance to cerebral blood flow; a low pi refers to significant advancing diastolic flow (low cerebral vascular resistance); a high pi refers to minimal advancing diastolic flow (high cerebral vascular resistance).Persistence of a hemodynamically significant patent ductus arteriosus (hsPDA) in preterm very low birth weight (VLBW) infants may increase the potential for cerebral injury due to left-to-right shunting of blood through the hsPDA and alterations in cerebral perfusion.

Preterm infants with a hsPDA have lower regional cerebral oxygenation levels and have a higher risk for intraventricular haemorrhage (IVH) and cerebral white matter injury^(14,15). Changes in cerebral perfusion pressure during ductal shunting and after ductal closure may predispose these infants to injury. Intact cerebral autoregulation maintains cerebral blood flow despite fluctuations in cerebral perfusion pressure, however preterm infants are more susceptible to altered cerebral autoregulation^(16,17).

Need For This Study

The occurrence of Circulatory disturbances during early neonatal period predispose to ischemic and haemorrhagic brain lesions in preterm infants, which have been associated with adverse neurological outcome in later life. As the PDA is considered to be the usual cause for elevated RI in preterms. Therefore, the proper hemodynamic evaluation and monitoring in Hemodynamically significant PDA preterm neonates can help significantly in overcoming the constraints and complication associated with these circulatory disturbances.

As Today more infants born at extremely low GA are treated than in prior years so this study aims to report RI values and then compare those values in various intracranial arteries and assess relationship between RI

values in hemodynamically significant PDA and nonPDA patients. So, doppler measurements can prove useful clinically for diagnostic, therapeutic and prognostic significance.

There is paucity of literature regarding the resistive indices in very preterm babies and only few studies have been published. Therefore, we decided to study the resistive index values of bilateral ICA, ACA and BA in very preterm infants and compare RI values between hemodynamic significant PDA cases and non/hisPDA cases.

Aims and objectives

To evaluate RI values of cerebral arteries in a prospective cohort of preterm infants less than 32 weeks of gestational age during stay in nicu and to compare RI values of cerebral arteries between neonates with hemodynamically significant PDA and those without PDA.

Methods

This was a prospective longitudinal study, written parental consent was obtained. We included all the preterm infants of less than 32weeks of gestational age admitted in NICU. Preterm infants with congenital malformations and chromosomal anomalies (patent ductus arteriosus was not considered a congenital malformation in this cohort of very preterm infants) were excluded from the study.

Imaging Protocol

Transcranial ultrasound and transthoracic echocardiographic examination

Transcranial ultrasound scanning was done by an experienced radiologist with 5 years in cranial ultrasonography. Images were obtained in the coronal plane through the using 8.0 mhz convex probe of sonosite m-turbo ultrasound system. Coronal plane images were taken and resistive indices of large arteries

were obtained and every artery was assessed roughly at the same level of their course for better comparison. The following intracranial vessels were examined which include bilateral internal carotid arteries, basilar artery and anterior cerebral artery. Doppler settings included pulse repetition frequency of 1.2khz, doppler frequency of 4mhz, gain of 71%, depth of 72mm. Resistive indices values of aforementioned arteries were calculated manually by measuring peak systolic velocity (psv) and end diastolic velocity (edv) with the help of formula: $ri = \frac{psv - edv}{psv}$. The Doppler assessment of every individual artery was performed on days 0,1,2 and 7 after birth and then weekly until discharge or death .subsequently all the preterm infants included in the study cohort were subjected to echocardiography on 3rd postnatal day for diagnosis of PDA. Tte was carried out using an apical four-chamber view, a left ventricular long-axis view, a right ventricular outflow tract view, using parasternal, apical, subxiphoid and supra-sternal approaches. The patent ductus arteriosus was diagnosed by cardiologist and the following criteria was deemed to label the PDA as hemodynamically significant which included, ductal size >2mm, left atrium to aortic root diameter of >1.6, and pulsatile flow pattern of patent ductus arteriosus. The patency and the direction of the ductal shunt were evaluated by colour flow mapping, with parasternal short axis view.

Stastical analysis

The data was analysed by the principal investigator with advice from a statistician. Descriptive data were analysed by frequencies and categorical data by percentages and continuous variables by means and standard deviations. Continuous variables were compared using student's t test (for parametric test) or mann-whitney u test (for non-parametric test) as appropriate. Group comparisons were

done by χ^2 tests. For qualitative data, chi-square test or fisher's exact test have been performed as appropriate.

For all comparisons, a p value of less than 0.05 was considered to indicate a statistical significance. All statistical analyses were done by the spss statistical software (release 23.0, spss inc.; chicago, iii).

Results

During the study period, 75 infants of less than 31 weeks of gestational age were admitted to the neonatal intensive care unit. Five (5) infants (with congenital malformations) were excluded, leaving 70 to be included. In our study we assessed resistive indices of intracerebral arteries and then compared the results in patients having hsPDA and those without PDA/hisPDA.

In our study among 70 preterm infants, 56 were with PDA and among them 18 cases were with hemodynamically significant PDA.

Table 1: Showing Presence and Absence of PDA and hsPDA in study Group

	HEMODYNAMICALLY SIGNIFICANT PDA		Total	P-value 0.009
	Absent	Present		
	PDA Absent	14 26.9%		
Present	38 73.1%	18 100.0%	56 80.0%	
	Total	52 100.0%	18 100.0%	

In our study among the 18 hsPDA patients, 14 cases (77.8%) were females and 4 cases (22.2%) were males. These results show positive correlation of hsPDA with female gender with a p-value of 0.013, With OR- 0.02 and 95%CI (0.02-0.009).

Table 2: Showing the Association of hsPDA with respect to gender

GENDER	HEMODYNAMICALLY SIGNIFICANT PDA		Total	p-value: 0.013 OR:0.02 95% CI (0.02-0.009)
	Absent	Present		
	M	30 57.7%		
F		22 42.3%	14 77.8%	
	Total	52 100.0%	18 100.0%	

In our study among the 18 hs PDA patients, 14 patients (77.8%) were females and 4 patients (22.2%) were males.

Table 3: Depicts the correlation of birth weight with respect to hsPDA

HEMODYNAMICALLY SIGNIFICANT PDA	N=no. of cases	Mean Birth weight (grams)	Standard Deviation	p-value 0.061
Absent	52	1063.8	0.12112	
Present	18	997.8	0.14265	

Resistive Indices Values Through Out the NICU Stay in the Study Group.

During the study period, one case with 26 weeks of gestational age reveal median RI values in Right ICA, Left ICA, ACA, BA were 0.85, 0.87, 0.84, 0.83 respectively. 5 cases were with 27 weeks of GA and median RI values of 0.84, 0.85, 0.83, 0.82 in Right ICA, Left ICA, ACA, BA were present respectively. 12 cases were having gestational age of 28 weeks and median RI values of 0.78, 0.79, 0.73, 0.72 in Right ICA, Left ICA, ACA, BA respectively were present. 10 cases were having GA of 29 weeks and median RI values of 0.77, 0.78, 0.73, 0.72 in Right ICA, Left ICA, ACA, BA was respectively. 34 cases were having GA of 30 weeks and median RI values of 0.78, 0.79, 0.75, 0.73 Right ICA, Left ICA, ACA, BA was present respectively. 8 cases

were with GA of 31 weeks in which median RI values of 0.76, 0.77, 0.74, 0.73 in Right ICA, Left ICA, ACA, BA were present respectively.(Table-1)

Table 4: Depicting the RI values corrected AGE median IQR

Gestational age (Weeks)	n = No. of patients	Right ICA Median (IQR)	Left ICA Median (IQR)	ACA Median (IQR)	Basilar Median (IQR)
26	1	0.85	0.87	0.84	0.83
27	5	0.84 (0.77-0.89)	0.85 (0.78-0.90)	0.83 (0.75-0.87)	0.82 (0.74-0.85)
28	12	0.78 (0.74-0.88)	0.79 (0.75-0.89)	0.76 (0.71-0.87)	0.73 (0.68-0.84)
29	10	0.77 (0.75-0.86)	0.78 (0.75-0.87)	0.73 (0.71-0.82)	0.72 (0.69-0.82)
30	34	0.78 (0.73-0.85)	0.79 (0.74-0.87)	0.75 (0.71-0.85)	0.73 (0.69-0.84)
31	8	0.76 (0.74-0.85)	0.77 (0.75-0.86)	0.74 (0.73-0.84)	0.73 (0.70-0.83)

When comparing resistive indices between Right ICA and Left ICA in hemodynamically significant and hemodynamically insignificant PDA cases, the mean resistive index values in Right ICA was 0.7665 ± 0.01959 in his/nonPDA cases and 0.8544 ± 0.01617 in hsPDA cases (p-value of <0.0001) which was statistically significant. The mean RI in Left ICA was 0.7777 ± 0.01926 in his/nonPDA and mean RI was 0.8667 ± 0.01495 in hsPDA (p-value <0.0001). (Table-2).While comparing resistive indices of Anterior cerebral arteries between hemodynamically significant and hemodynamically insignificant PDA patients, the mean RI of 0.8422 ± 0.01801 in hsPDA and mean RI value in his/nonPDA was 0.7429 ± 0.02172 (p-value ≤ 0.0001) which was statistically significant with 95% CI of -0.11072 to -0.08796. (Table-2) and while comparing resistive indices values of Basilar artery between hemodynamically significant and hemodynamically insignificant PDA patients. The resistive indices were on higher side in hsPDA cases with (p-value of ≤ 0.0001) which was statistically significant and 95% CI of -0.11791 to -0.09324. In his/nonPDA cases the mean RI

value was 0.7194 ± 0.02437 and in hsPDA cases mean RI was 0.8250 ± 0.01618 . (Table-2) In our study among 70 cases 26 cases (37.1%) got expired among which 10 cases (55.6%) were with hsPDA and 16(30.8%) were hisPDA/non-PDA cases.

Table 5: Resistive indices values throughout the NICU stay: RI values for postnatal AGE median IQR

Postnatal age (weeks)	Right ICA	Left ICA	ACA	Basilar Artery
0	0.77 (0.73-0.80)	0.78 (0.74-0.80)	0.73 (0.71-0.79)	0.72 (0.69-0.76)
1	0.77 (0.74-0.88)	0.79 (0.75-0.89)	0.75 (0.71-0.87)	0.73 (0.69-0.84)
2	0.78 (0.74-0.87)	0.79 (0.75-0.88)	0.77 (0.71-0.87)	0.76 (0.68-0.84)
3	0.78 (0.73-0.89)	0.79 (0.74-0.90)	0.75 (0.71-0.87)	0.72 (0.69-0.85)

Table 6: Depicting the outcome in hemodynamically significant PDA

Outcome	HEMODYNAMICALLY SIGNIFICANT PDA		Total	p-value: 0.050
	Absent	Present		
Discharge	36	8	44	OR:3.4
	69.2%	44.4%	62.9%	
Death	16	10	26	95%CI: 0.93-8.45
	30.8%	55.6%	37.1%	
Total	52	18	70	
	100.0%	100.0%	100.0%	

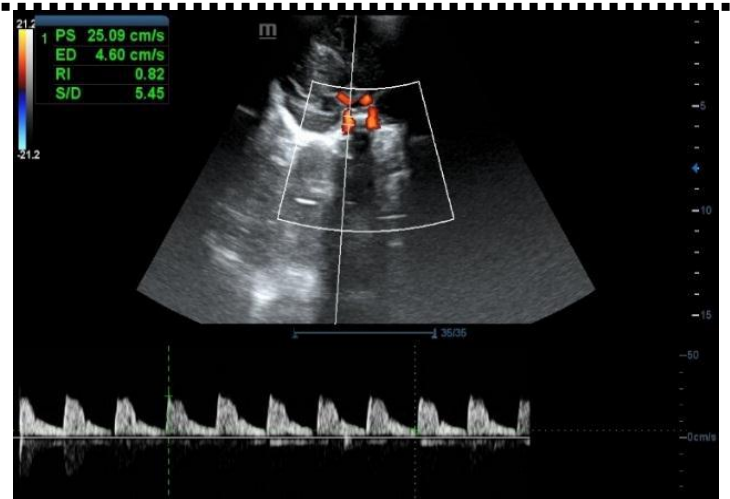
Representative Cases

Fig. 1-4: Colour Doppler Images of Left Internal Carotid artery, Right internal Carotid artery, basilar artery, and anterior cerebral artery depicting the high and low resistance flow in hsPDA and hisPDA Cases respectively.

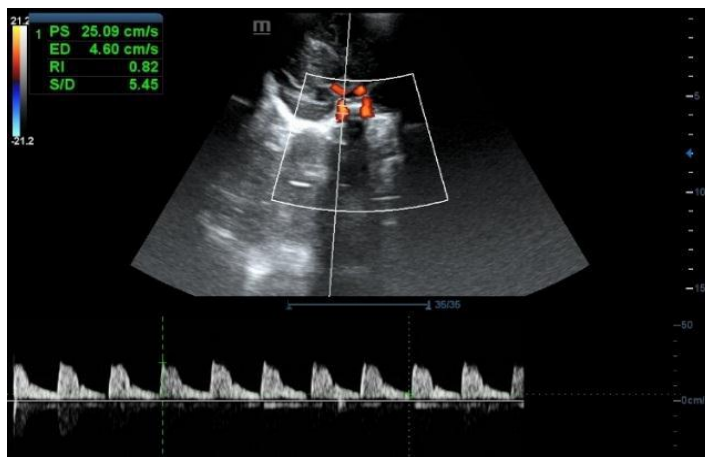
Fig. 1: Colour Doppler USG Image of Left Internal Carotid artery.



1(a): Depicting low resistance flow in hisPDA preterm infant.

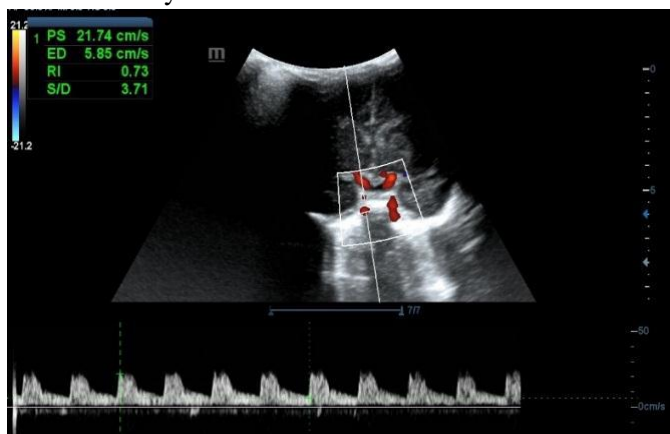


2(b): Depicting high resistance flow in hsPDA preterm infant.



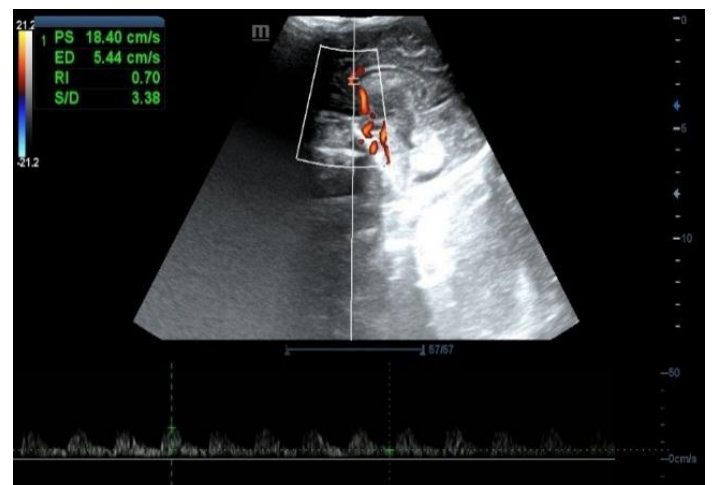
1(b): Depicting high resistance flow in hsPDA preterm infant.

Fig. 2: Colour Doppler USG Image of Right Internal Carotid Artery

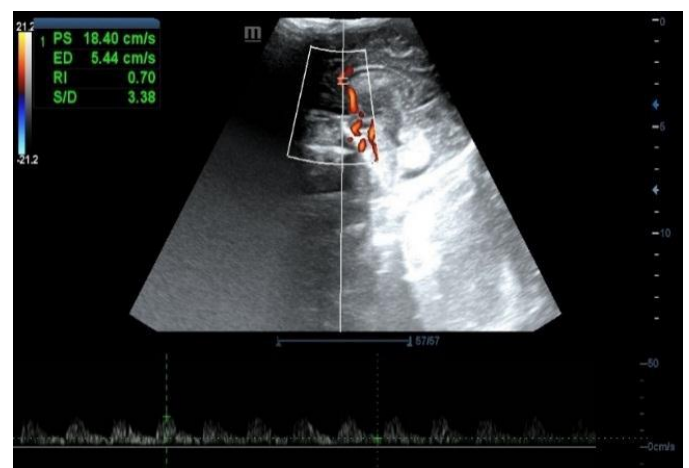


2 (a): Depicting low resistance flow in hisPDA preterm infant.

Fig. 3: Colour Doppler USG Image of ACA

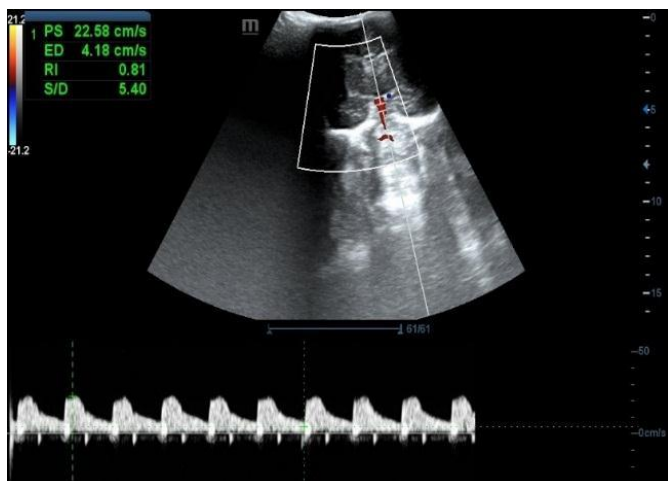


3(a): Depicting low resistance flow in hisPDA preterm infant.

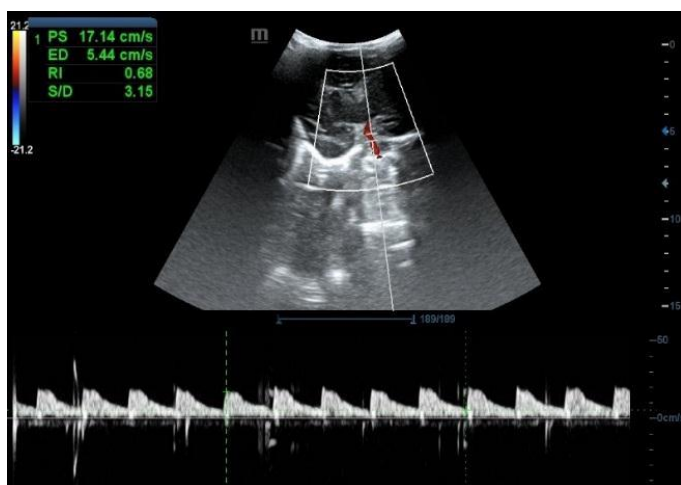


3(b): Depicting high resistance flow in hsPDA preterm infant.

Fig. 4: Colour Doppler USG Image of Basilar Artery.



4(a): Depicting low resistance flow in hsPDA preterm infant.



4 (b): Depicting high resistance flow in hsPDA preterm infant.

Discussion

We found that the resistive indices values differed among the arteries. RI values differed depending on the artery which was insonated. We took large arteries into account including Right Internal carotid, Left Internal carotid, Anterior Cerebral artery and Basilar artery. The RI values were calculated and then compared between hemodynamically significant PDA Cases and hemodynamically insignificant PDA/non-PDA cases.

The mean RI value calculated in Right ICA in the study group was 0.7891 (ranging from 0.73- 0.89) \pm 0. 0195.

The mean RI values calculated in hisPDA were 0.7665 ± 0.01995 and in hsPDA patients the mean RI values calculated were 0.8544 ± 0.01617 (p-value ≤ 0.0001) which is considered statistically significant. The mean RI values calculated in Left ICA in hisPDA were 0.7777 ± 0.019260 and in hsPDA patients the mean RI values calculated were 0.8667 ± 0.01495 with p-value (≤ 0.0001) which is considered statistically significant. while comparing resistive index values between Right ICA and Left ICA in hemodynamically significant and hemodynamically insignificant PDA patients, the resistive indices were on higher side in hsPDA cases with p-value (< 0.0001) which was statistically significant. The difference of RI values in Right ICA and Left ICA was statistically insignificant, though slightly higher values were present in left ICA. Our study is complemented by many previous studies, **Ecury et al**⁽¹⁹⁾ calculated resistive indices among different arteries, they found high RI values in hsPDA as compared to hisPDA patients in both Right ICA and Left ICA, they also found that Left ICA values were on higher side compared to right ICA. **Pezzati et al**,⁽¹⁸⁾ carried out the study on infants < 34 weeks GA, they found that there was significant difference in RI values between Right ICA and Left ICA with respect to PDA, which in turn is reflected by alterations in cerebral blood flow.

The mean RI values in ACA were 0.7891 (ranging from 0.73-0.89). The mean resistive indices in hisPDA patients were 0.7429 ± 0.02172 and the mean resistive indices values in hsPDA patients were 0.8422 ± 0.01801 . The RI values were on a higher side in hsPDA patients as compared to his/nonPDA patients with p-value (< 0.0001). The results of our study were in concordance with many previous studies. **Mires et al**,⁽²⁰⁾ conducted a longitudinal study in preterm infants, they found that RI

values were significantly higher in ACA in hsPDA patients with mean RI of 0.78 with p-value (<0.01).

The mean RI values in Basilar artery were 0.746 (ranging from 0.680-0.85). The mean resistive indices in hisPDA patients were 0.7194 ± 0.02437 and the mean resistive indices values in hsPDA patients were 0.8250 ± 0.01618 . The RI values were on the higher side in hsPDA patients as compared to hisPDA patients with p-value (<0.0001).

The results of our study were in concordance with many previous studies. Mires et al,⁽²⁰⁾ found that RI values were significantly higher in Basilar arteries in hsPDA patients with mean RI of 0.79 with p-value (<0.001). Ecury Goossen et al⁽¹⁹⁾ conducted a study in preterm infants to compare RI values in various intracranial arteries, they found that RI values were consistently higher in hsPDA patients with mean of 0.79 than hisPDA patients with median of 0.66 p-value (<0.001).

Outcome of study group

In our study among 70 cases, 26 patients (37.1%) expired among which 10 patients (55.6%) were having hsPDA and 16 patients (30.8%) were hisPDA/nonPDA. We found that more preterm infants with hsPDA expired as compared to hisPDA/non-PDA patients (55.6% vs 30%, p-value 0.06). This was attributed to more respiratory and cerebral complications associated with hsPDA. Our results were in complete agreement with studies done by Okur et al. and Visconti et al^(22,23) which found that preterm cases with hsPDA are associated with higher mortality rate than hisPDA patients.

Summary and Conclusion

Our study gives the resistive indices of cerebral arteries in preterm infants < 32 weeks of gestational age and compared results in patients with hsPDA and his/nonPDA. We found that resistive indices were slightly higher in hsPDA cases. Germinal Matrix Haemorrhage / IVH, Sepsis, RDS, BPD, NEC and

mortality was more in preterm infants with hemodynamically significant PDA.

Abbreviations : PDA- Patent Ductus arteriosus, RI- Resistive index, TTE- Transthoracic Echocardiography.

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