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The Role of Trans Cranial Doppler Ultrasonography as an Alternative Predictor for Hemodynamic Significance of Persistent Ductus Arteriosus in Preterm Neonates

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Abstract

Failure of postnatal closure of ductus arteriosus (DA) in preterm infants may lead to clinical symptoms of an open-angle DA (PDA) that are hemodynamically significant and need treatment. As a result of the decreased blood supply to essential organs and the resulting alterations in cerebral blood flow, brain damage is possible. Using cranial Doppler ultrasonography, this research was able to measure the cerebral hemodynamic consequences of PDA and its correlation to the prognosis. After 24 hours, clinical parameters and transcranial Doppler of the anterior cerebral artery were assessed and divided into two groups: HS PDA (hemorodynamically significant) and HIS PDA (hemorodynamically insignificant) based on clinical deterioration after 72 hours. 71 preterm neonates were included in the study. There is a high correlation between the resistive index (RI) and the clinical worsening of hemodynamically significant patients. Aside from clinical measures and echocardiography, the results of this research show that the trans-cranial Doppler is an effective bedside technique for predicting hemodynamically significant PDA in preterm infants before clinical parameters deteriorate and avoids further clinical deterioration. For preterm infants, we suggest cranial Doppler scanning as soon as possible.

Keywords: Trans Cranial, Ultrasonography, Preterm Neonates, PDA, Reistive index.

1.Introduction

Within 72 hours after birth, 90 percent of 30 week gestational age babies have closed their patent arteriosus (PDA) shunts, but it may remain open in unwell or preterm children for many months if they are unable to seal the PDA within this time frame [1]. Preterm delivery is associated with an increased risk of developing a clinically significant patent ductus arteriosus that necessitates treatment due to ductus arteriosus failure occurring postnatally [2].

Because of the considerable left-to-right flow via the patent ductus, which may cause decreased blood supply to the systemic circulation, particularly in the brain, lungs and digestive tract of ill preterm infants; this can lead to organ failure [3].

There is no consensus on how to determine whether or not a Patent ductus arteriosus is hemodynamically relevant. However, clinical indications including elevated pulse pressure, tachycardia, and metabolic acidosis may take longer to appear. It's still widely used as a metric for determining if a premature baby has to have a Patent Ductus Arteriosus (PDA) closed [4].

There is a need for additional clinical and biochemical criteria for risk stratification since echocardiography alone at 48 hours of birth cannot identify babies with a Patent ductus arteriosus who go on to have severe intraventricular haemorrhage and/or die [5].

Hemodynamics may be monitored in newborn hospitals using Doppler sonography, which is a noninvasive technique. When evaluating cerebral hemodynamic alterations in extremely low birth weight newborns, it might be beneficial to look for Patent ductus arteriosus (PDA), which has an elevated resistive index (RI) and a reduced diastolic velocity (DV). Reducing resistance index and increasing diastolic velocity indicate that the Patent ductus arteriosus has been closed [6].

The goal of this study is to determine if trans cranial Doppler ultrasound (TCDUS) can predict hemodynamically significant PDA in preterm neonates before clinical parameters deteriorate, which may aid in the selection of a treatment plan and prevent further clinical deterioration (FECHO).

2.Patients and methods

This prospective cohort study was conducted in the Neonatal Intensive Care Unit, (NICU) of the pediatric department in Mit Ghamr General Hospital. The period of the study extended for 8 months (from January 2021 till August 2021). The study included 71 preterm neonates <36 weeks GA were evaluated by Echocardiography for the presence of PDA then clinical parameters assessment and Trans cranial Doppler ultrasonography were done in the first 24 hours of life then all neonates were reassessed after 72

hours with both clinical parameters (HR, pulse pressure, metabolic acidosis) and RI and divided into two groups based on the clinical deterioration after 72 hours: **Group 1:** 47 neonates with hemodynamic significant (HS) PDA. and **Group 2:** 24 neonates with hemodynamic insignificant (HIS) PDA.

2.1. Inclusion criteria:

 GA <36 weeks Both genders are included.

2.2. Exclusion criteria:

The presence of sepsis or any cardiac defects (including a patent foramen ovale (PFO) > 3 mm) that could alter the hemodynamic status of the patients.

The selected subjects (n=71) were subjected to the following from day 1 to day 4 of life:

1. **Full history taking**
2. **Complete physical examination and arterial blood gases:**
3. **Cranial Ultrasound and Doppler: ***

Hemodynamic assessment:

Cerebral blood flow velocity recordings were made by color duplex Doppler module of cranial ultrasound apparatus manufactured by Sonosite. We used 5-12 MHz frequency sectorial transducers. The high-pass filter, used to remove low frequency noise was set at the level of 50-100 Hz. Recordings of CBF velocities were made in the supine position. Observations were made when the infants are in a quiet state, with no gross body movements.

Anterior cerebral artery was visualized in the sagittal plane through the anterior fontanel and the signals were recorded from the point midway between the inferior-most border of the corpus callosum and the vessel origin from the circle of Willis.

The angle correction was performed and the angle was always less than 30° to minimize the Doppler shift measurement error. The data reported represented the average of three determinations. We measured the peak systolic velocity (PSV), end-diastolic velocity (EDV). The resistive index (RI) was calculated according to the formula RI = (PSV-EDV)/PSV).

*** Morphological assessment:**

Cranial ultrasound imaging was performed via the anterior fontanel, imaging included both sagittal and coronal planes.

4.Targeted neonatal Echocardiography (TNE)/FECHO Functional was performed:

TNE/FECHO was done for each case according to combined American and European guidelines. All studies were performed for all cases in a supine or left lateral position using Sonosite apparatus with 6 MHz neonatal multifrequency transducer having tissue velocity imaging capabilities. The examination consisted of 2D, M-mode, 2-D, pulsed, continuous wave and color Doppler blood flow velocity. 2D Echocardiography to determine the presence of

3.Results

PDA from suprasternal ductal view as well as short axis parasternal view.

Each study consisted of :

a) Assessment of SVC flow by assessment Velocity Time Integral (VTI) of SVC, obtaining mean SVC diameter to calculate SVC flow by the following equation:

(Heart rate x mean SVC cross sectional area x SVC VTI)

Body weight.

SVC diameter was obtained from the high suprasternal view while the SVC VTI was obtained from the subcostal view. A mean value was obtained for the SVC VTI and diameter from 5 cardiac cycles.

b) Assessment of LV outflow (LVOF) by assessment VTI of Aorta, aortic diameter by the following equation:

(Heart rate x aortic cross sectional area x aortic VTI)

Body weight

Aortic diameter was obtained from the Parasternal long axis view while the Aortic VTI was obtained from the apical five-chamber view by pulsed wave Doppler.

c) LA/Ao ratio.

Functional Echocardiography was performed each time by the cardiologist (trained to perform the above mentioned protocol of TNE and blinded to the clinical data) to test variability of each measure and reliability of use of each index as a predictor to hemodynamic significance of PDA by Kappa coefficient.

2.3Statistical analysis:

All data was retrieved from files, collected, tabulated and analyzed using the Statistical Package for Social Science (SPSS) version 15. The following methods were employed: Mean and standard deviation (SD) or median and interquartile range (IQR) were estimates of quantitative data, while frequency and percentage were estimates of qualitative data. Differences in clinical and biochemical characteristics were tested by Student's paired and unpaired t-test, Mann-Whitney U test or Wilcoxon test for quantitative data and by Chi-square test for qualitative data. Receiver-operating characteristic (ROC) curve analysis was used to examine the value of RI, SVCF, RVOF, or L VOF in prediction

of patients with hemodynamically significant PDA and in early discrimination of patients with hemodynamic significant PDA from patients with hemodynamic insignificant PDA. P values less than 0.05 were considered statistically significant.

Table (1) Comparison between the values of clinical parameters between HS & HIS PDA.

Clinical measurements		PDA HS	PDA HIS	P-value
Lactate	Mean	1.494	1.383	0.211
	SD	0.419	0.439	
	Minimum	1.00	1.00	
	Median	1.40	1.20	
	Maximum	3.00	2.30	
Pulse pressure	Mean	11.936	12.378	0.366
	SD	1.58	2.464	
	Minimum	10.00	10.00	
	Median	12.00	12.00	
	Maximum	16.00	22.00	
UO	Mean	3.785	3.817	0.975
	SD	0.548	0.632	
	Minimum	2.40	2.80	
	Median	3.90	3.80	
	Maximum	5.00	5.10	
HR	Mean	133.06 7.25	132.54 9.60	0.798
	SD	122.00	115.00	
	Minimum			
	Median	133.00	133.00	
	Maximum	162.00	155.00	

Table (2) The ultrasonography findings in first 24 hours.

Ultrasonography findings	PDA HS (n=47) Count	%	PDA HIS (n-24) Count	%
No	15	32%	23	95.8%
Ischemia	26	55%	-	0%
Intracranial hemorrhage	2	4%	1	4.2%

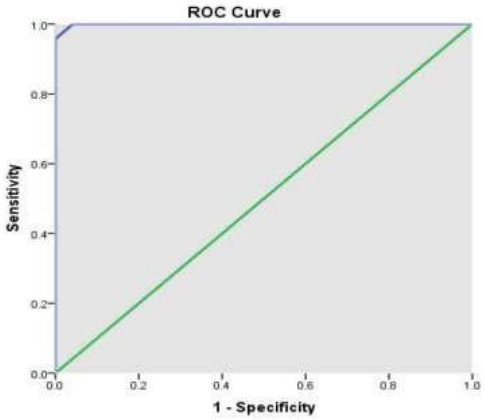

Fig. (1) ROC curve for RI in the first 24 hours.

For the ultrasonographic findings, Table (2) shows that there were value 32% of hemodynamic significant (HS) cases (cases with significant left to right shunt through the PDA)

In this study, we consider the data consists of 71 nenoates.These gestational aged ranged from 28 to 35 weeks with mean value 32.42 weeks and standard deviation 0.244. They were divided into two groups. Group 1: 47 neonates with HS PDA & Group 2: 24 neonates with HIS PDA according to clinical deterioration after 72 hours. There is no significant difference between groups regarding clinical parameters [Lactate, Pulse Pressure, Urine output (UO) and Heart rate (HR)] , table (1).

having abnormal ultrasonographic findings and about 84% of them appeared to have ischemia, also there were 13% of hemodynamic significant cases appeared to have intracranial hemorrhage. However, for the hemodynamic insignificant (HIS) cases, there were about 95.8% of total case had no abnormal ultrasonographic findings and only one case appeare to have intracranial hemorrhage.

On analysis after 72 hours:

According to RI, the HS results appeared to have greater mean value 0.812 (+0.17/-0.11) than the HIS result which has mean value 0.629 (+0.07/0.23). Comparing the mean values of RI between HS and HIS observed values using t-test, we conclude that there is a significant difference between the two means at 5% significance level. Also, for LVO/SVC, we conclude that there is a significant difference between the two means at 5% significance level. For LA/Ao and ductal size parameters, we conclude that there is no significant differene between the two means at 5% significance level. table 3

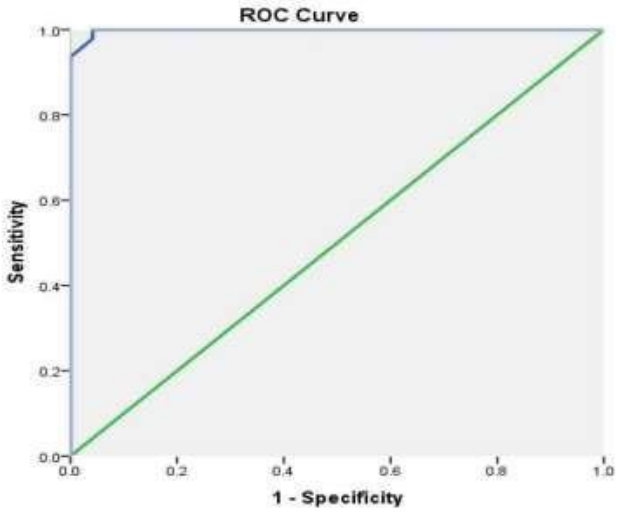

Fig. (2) ROC curve for RI after 72 hours.

Table (3) Comparison of the resistive index and echocardiographic parameters values between HS & HIS PDA.

Variables			PDA HS	PDA HIS	P-value
RI		Mean	0.812	0.629	<0.001
		SD	0.039	0.063	
		Minimum	0.70	0.40	
		Median	0.80	0.645	
		Maximum	0.98	0.70	
Ultrasonographic parameters	LVO/SVC	Mean	2.609	1.175	<0.001
		SD	0.84 1.10	0.219	
		Minimum Median	2.00 3.20	0.90 1.15	
		Maximum	1.121 0.225	2.10	
	La/Ao	Mean	0.80	1.105 0.185	0.044
		SD	1.00	0.70	
		Minimum		1.00	
		Median			
		Maximum	1.60	1.30	
	Ducted	Mean	2.702 1.012	2.275 0.709	0.053
		SD	1.30	1.30	
		Minimum size	2.80	2.10	
		Median			
		Maximum	5.00	4.00	

The gap between HS and HIS results for all clinical parameters after 72 hours increases with significant difference as compared to the results obtained in the first 24 hours results. table 4

Table (5) shows that there were about 30% of hemodynamic significant (HS) cases having to abnormal ultrasonographic findings and about 66% of them appeared to have ischemia, also there were 13% of hemodynamic significant cases appared to have intracranial hemorrhage. However, for the hemodynamic insignificant (HIS) cases, there were about 95.8% of total cases had no abnormal ultrasonographic findings and only one cases appeare to have intracranial hemorrhage. So our study shows that not only early RI changes in the first 24 hours are predictive of ulterior clinical deterioration in the next days but it also highlighted that ultrasonographic findings such as ischemia and hemorrhagic infarctions occur early in patients with subsequent clinical deterioration. Suggesting that cerebral vasomotor instability coupled or triggered by the presence of PDA might precade hemodynamic instability affecting other organs. Patients that have ultrasonographic findings of ischemia in the first 24 hours despite normal Sarnat staging, After 72 hours they displayed signs of

Table (4) Comparison between the values of clinical parameters after 72 hours between HS & HIS PDA.

Clinical measurements		PDA		P-value
		HS	HIS	
Lactate	Mean	6.872	2.542	<0.001
	SD	1.279	1.56	
	Minimum	4.00	0.00	
	Median	7.00	2.00	
	Maximum	10.00	8.00	
Pulse pressure	Mean	29.34 3.737	16.042	<0.001
	SD	22.00	2.726	
	Minimum		13.00	
	Median	28.00	15.50	
	Maximum	38.00	24.00	
UO	Mean	1.47	2.83	<0.001
	SD	0.495	0.582	
	Minimum	0.90	2.20	
	Median	1.40	3.00	
	Maximum	3.20	4.20	
HR	Mean	178.51 11.72	125.63 5.14	<0.001
	SD	144.00	116.00	
	Minimum			
	Median	177.00	125.00	
	Maximum	210.0	140.00	

Table (5) The ultrasonography findings after 24 hours.

Ultrasonography findings	PDA			
	HS (n=47)		HIS (n-24)	
	Count	%	Count	%
No	14	30%	23	95.8%
Ischemia	27	57%	-	0%
Intracranial hemorrhage	2	4%	1	4.2%
Ischemia & intracranial hemorrhage	4	9%	-	0%

Table (6) Comparison of the resistive index values after 72 hours between HS & HIS PDA.

Variables		PDA		P-value
		HS	HIS	
RI	Mean	0.889	0.638 0.059	<0.001
	SD	0.044	0.55	
	Minimum	0.77		
	Median	0.90	0.63	
	Maximum	0.99	0.78	

brain ischemia with rise of their Sarnat score which also proved that ultrasonopgraphic findings of brain ischemia may precede that actual clinical manifestatiuons of brain ischemia.

According to RI, the HS results appeared to have greater mean value 0.889 (+0.1/-0.12) than the HIS result which has mean value 0.638 (+0.142/0.089). Comparing the mean values of RI between HS and HIS observed values using t-test, we obtain P-value of <0.001; so we concluded that there is significant difference between the two means at 5% significance level. table 6

ROC for RI of both HS and IDS groups in the first 24 hours, presented in figure 1, the AUC of RI was 99.9% producing a significant p-value of <0.001. The RI had a sensitivity of 100% and specificity of 100% this conclusion confirms that RI is a good predictor of subsequent clinical deterioration of patients with PDA. Also that 0.70 represents the cutoff value of resistive index, this conclusion enables us to make a prediction that if RI value is greater than 0.70 we will have a hemodynamic significant (HS) PDA and vice versa, if RI value is less than 0.70 we will have a hemodynamic insignificant (HIS) PDA.

ROC for RI of both HS and IDS groups after 72 hours , presented in figure 2 ,we recognize that 0.77 represents the cutoff value of resistive index. Also the AUC of RI was 99.8% producing again a significant p-value of <0.001, also the resistive index had a sensitivity of 100% and specificity of 100%.

Fig.(3) Coronal image of CDS.

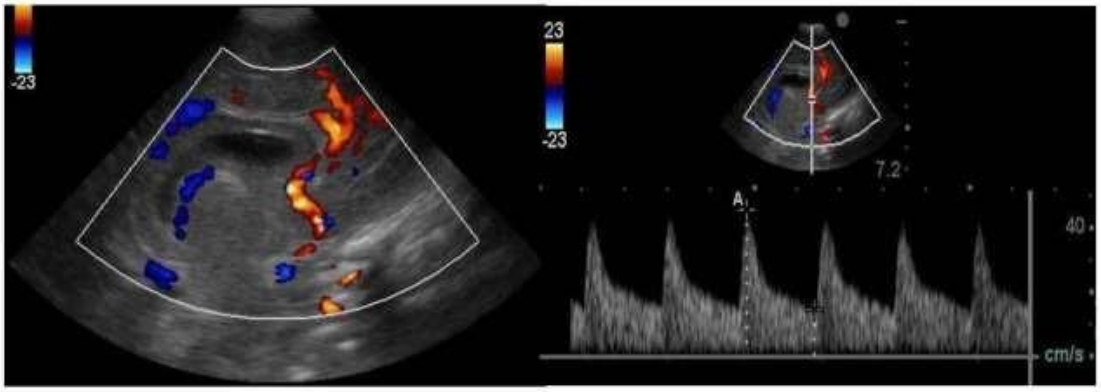

Fig.(4) Mid-sagittal image with Doppler of ACA (Day 1).

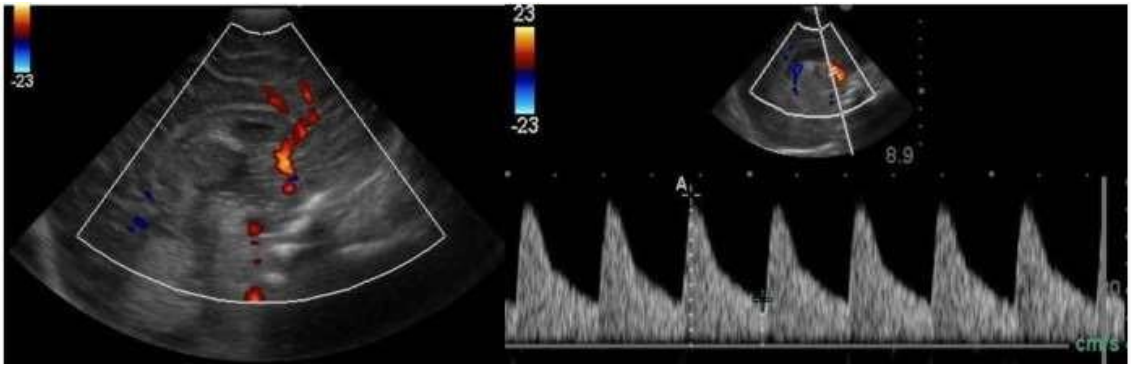

Fig.(5) Follow up Doppler ACA.

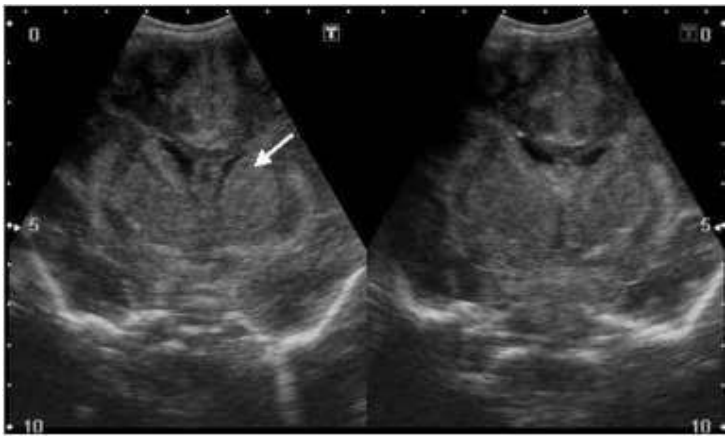

Fig.(6) Coronal image of CUS showing echogenic thalami.

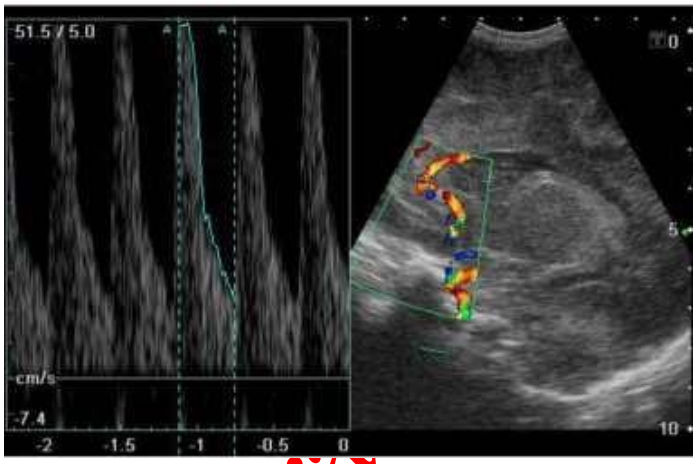

Fig.(7) Mid sagittal image with Doppler of ACA (Day 1).

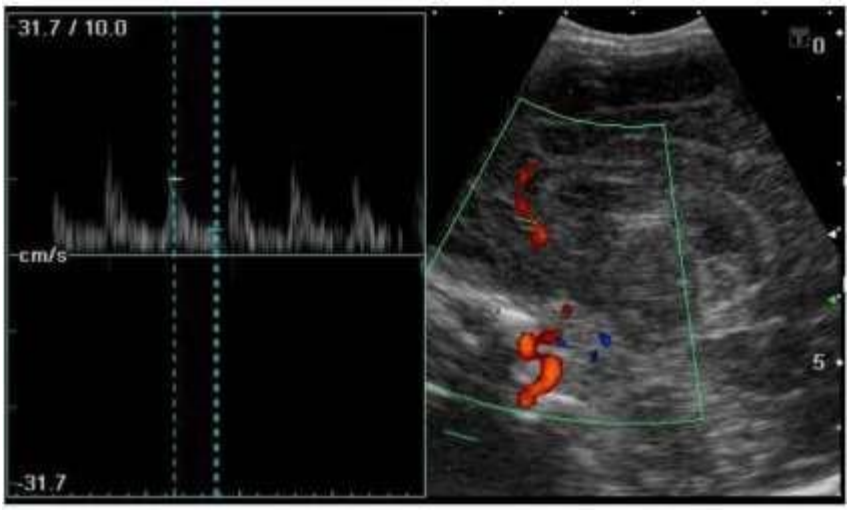

Fig.(8) Follow up Doppler ACA.

Case 1: A female preterm, gestational age 32 weeks, birth weight 1.5 kilograms, was transferred to NICU. At the first 24 hours of life: Echocardiography was done and revealed: LVO/SVF: 1.2 ,LA/Ao: 0.78, Ductal size: 1.5 . Clinical parameters were assessed and revealed: Lactate: 1.5, Pulse pressure: 11, Urine output: 3.2, Heart rate: 124. Trans-cranial Doppler for ACA was done, revealed RI of 0.68 . Cranial Ultrasonographic findings: Normal CUS. figure 3,4

Follow up after 72 hours: Clinical parameters; Lactate: 2, Pulse pressure: 19, Urine output: 2.4, Heart rate: 123. Trans-cranial Doppler for ACA was done revealed RI of 0.69. figure 5

Opinion: Findings are suggestive of Hemodynamic insignificant (HIS) PDA.

Case 2: A male preterm, gestational age 31 weeks, birth weight 1.25 kilograms, was transferred to NICU. At the first 24 hours of life: Echocardiography was done and revealed: LVO/SVF: 1.6, LA/Ao: 0.8, Ductal size: 1.3. Clinical parameters were assessed and revealed: Lactate: 2, Pulse pressure: 12, Urine output: 4.1, Heart rate: 138. Trans-cranial Doppler for ACA was done, revealed RI of 0.77. Cranial Ultrasonographic findings: Ischemia in the form of echogenic thalami and both gangliafigure 6,7 ,

Follow up after 72 hours: Clinical parameters; Lactate: 6, Pulse pressure: 33, Urine output: 1.4, Heart rate: 178. Trans-cranial Doppler for ACA was done revealed RI of 0.8, figure 8

Opinion: Hemodynamic significant (HS) PDA with sonographic findings suggestive of Ischemia.

4. Discussion

It was shown that there was a significant difference between the two groups of PDA when it came to clinical indicators such as lactate, pulse pressure, urine output, and heart rate (HR) as well as resistive indices (RI). Even after 72 hours, there remained a statistically significant difference between our two groups when it came to clinical parameters. This led us to conclude that clinical measures alone cannot identify substantial PDA in the first 24 hours of life. Davis et al [7] also observed that all clinical measures might be somewhat delayed, which is in agreement with our results. [7]. In their investigation, Skelton et al. [8] also found that the use of this clinical symptom to diagnosis a large PDA might lead to considerable inaccuracy. In the first 24 hours, all echocardiographic parameters seemed to have a larger mean value for the HS group than the HIS group, according to our findings. There was a significant P-value of 0.001 for the LVO/SVC parameter of the Receiver operating characteristic (ROC) curve, with a 95% confidence interval of 0.862-0.989, and a non-significant P-value of 0.0831 for the LA/Ao parameter of 0.626, both with 95% confidence intervals of 0.496-0.757. The AUC of the ductal size parameter was 0.582, with a 95 percent confidence interval ranging from 0.445 to 0.718, and a non-significant Pvalue of 0.263, for Ductal Size parameter. LVO/SVC seems to have the best significant pvalue with the greatest values for both sensitivity and specificity as the only echocardiographic measure that may predict in the first 24 hours hemodynamically significant PDA according to our data. This finding contradicts the findings of El-Khuffash et al. [5], who found that echocardiography alone at 48 hours could not identify babies with a PDA who suffered from severe intraventricular haemorrhage (IVH) or died. It was also shown that no echocardiographic measure would be predictive of hemodynamic importance to the degree that it will change clinical decision-making. In contrast, we found that the LVO/SVC ratio, which is unaffected by trans atrial flow, may be a more accurate indicator of ductal flow than other markers, such as the LA:Ao ratio, which was shown to be effective in the identification of a substantial PDA in preterm children by Hajjar et al. [10]. Anterior cerebral artery resistive index (RI) was higher in the HS group (0.812 with SD 0.039) than in the HIS group (0.812 with SD 0.039) over the first 24 hours of the PDA study in both groups (0.629 with SD 0.0625). It was also shown that the RI after 72 hours in the HS PDA group was bigger than in the HIS group (0.889 with SD 0.0438). (mean value 0.638 with SD 0.0599). We found that the AUC of RI was 99.9%, which had a significant p-value of 0.001. The RI's sensitivity and specificity were both 100%. This result permits us to anticipate that if the resistive index (RI) value is more than the cutoff, we have a hemodynamically significant (HS) PDA, and vice versa, since 0.70 is the cutoff value for the first 24 hours and 0.77 is the cutoff for RI after 72 hours.

In this study, we found that cranial Doppler sonography is a valuable method for assessing changes in cerebral hemodynamics in VLBW babies with PDA. ACA diastolic velocity (Vd) decreases with increased RI, which suggests a PDA. RI and Vd normalisation indicates that the PDA has closed. These findings were corroborated by other researchers, including Baytur et al [12], who discovered that premature babies with respiratory distress syndrome had decreased diastolic blood flow velocities and increased resistance indices due to patent-ductus syndrome. Gothelf et al [13] found that premature babies with respiratory distress syndrome had increased RI along with decreased diastolic amplitude and velocity.

5. Conclusion

Preterm infants with a hemodynamically significant PDA who had RI values were able to predict clinical worsening. Trans-cranial Doppler (TCD) may be used to predict hemodynamically significant (HS) PDA in preterm infants prior to the worsening of clinical parameters, as shown in this study.

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