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Original article

Doppler evaluation of renal blood flow as a predictive index of acute renal failure in perinatal asphyxia

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Abstract

Background: Renal involvement is a common occurrence in perinatal asphyxia. Till date, only a handful of studies from across the globe have evaluated the use of renal Doppler as a predictive modality for acute kidney injury (AKI) in birth asphyxia.

Aims: To evaluate the role of Doppler study of renal blood flow in predicting acute renal failure in perinatal asphyxia.

Settings and design: This was a prospective cohort study.

Materials and methods: 30 preterm and term neonates with perinatal asphyxia defined as an Apgar score of 0-3 at 1 minute and cord pH of ≤ 7.00 or base deficit of > 16 mmol/L and 30 healthy neonates matched for gestational and postnatal age were enrolled. Renal blood flow parameters were studied on the 1st day and the 3rd day. Serum creatinine was taken as the gold standard for defining AKI.

Statistical analysis used: Receiver operating characteristics (ROC) was used to evaluate the diagnostic performance of renal Doppler. SPSS® version 17.0 was used.

Results: The ROC curves obtained for all the renal blood flow parameters on day 1 and day 3 to see the utility of the renal Doppler ultrasonography in predicting acute renal failure in severe birth asphyxia revealed that the area under the curve (AUC) was not significant for any of the parameters.

Conclusions: Contrary to the results seen in the previous studies, this study indicates that renal blood flow parameters may not be a useful modality to predict the occurrence of AKI in perinatal asphyxia.

Keywords

Perinatal asphyxia, renal blood flow, renal Doppler, resistive index, acute kidney failure.

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Introduction

Birth asphyxia is a leading cause of neonatal mortality [1]. Child Health Epidemiology Reference Group (CHERG), now known as Maternal and Child Epidemiology Estimation group (MCEE) estimates that, in 2013, intrapartum-related neonatal deaths were the third leading cause of death in children younger than 5 years, accounting for approximately 662,000 deaths, or 10.5% of deaths in children younger than 5 years and 24% of neonatal deaths [2].

Birth asphyxia leads to hypoxic injury to the major organs including the brain, heart, kidneys, liver, lungs and the gastrointestinal system. Kidneys are frequently involved in birth asphyxia with a prevalence of 56% [3]. Acute kidney injury (AKI) in birth asphyxia can further complicate the management of an asphyxiated newborn and can result in severe morbidity as well as mortality. Renal artery Doppler measurements have been studied as a non-invasive diagnostic tool to predict renal involvement in neonates with birth asphyxia [4, 5]. Till date, only a handful of studies from across the globe and none from India have evaluated the use of renal Doppler as a predictive modality for AKI in birth asphyxia neonates. Hence, this study was planned to assess if a non-invasive modality such as renal Doppler helps predict the occurrence of renal failure in asphyxiated neonates.

Materials and methods

This was a prospective cohort study conducted in a tertiary care hospital from January 2015 to May 2016.

Inclusion criteria

All preterm and term neonates with severe birth asphyxia defined as an Apgar score of 0-3 at 1 minute and cord pH of ≤ 7.00 or base deficit of > 16 mmol/L.

Exclusion criteria

1. Neonates with major congenital malformations and chromosomal anomalies;
2. neonates with renal malformations detected antenatally or postnatally;
3. neonates with suspected sepsis.

Methodology

The participation was voluntary and written informed consent was taken from the parent or guardian of the baby. The Institutional Ethical Committee approved the study protocol.

The Doppler studies of renal blood flow velocities were conducted on day 1 and day 3. The first renal Doppler was conducted after the first 2 hours of life. The blood flow velocities were studied in 2 windows: 2-24 hours and 48-72 hours. Toshiba model UICW – 580A was used for doing the renal Doppler ultrasonography. The artery was sampled at 5-10 mm from the abdominal aorta at an insonation angle as low as possible. After a stable velocity recording of more than 10 consecutive beats, 3 consecutive waveforms with the highest possible velocities were taken for peak systolic velocity (PSV) and end diastolic velocity (EDV). The resistive index (RI) [6] was then calculated: RI = PSV - EDV / PSV

The neonate was monitored clinically for acute renal failure by monitoring urine output 8-hourly, weight daily and serum creatinine and blood urea after day 2. Oliguria was defined as a urine output of < 1 mL/kg/h. Urine output was quantified by estimating the diaper weight. Blood urea was measured by the enzymatic method. Serum creatinine was measured by Jaffe's method.

Acute renal failure was defined as [7-9]:

1. serum creatinine > 1.5 mg/dL for at least 24-48 hours if the mothers renal function is normal;
2. serum creatinine more than 0.3 mg/dL over baseline;
3. serum creatinine fails to fall below the maternal plasma creatinine within 5-7 days.

For this study, a convenient sample size of 30 neonates with severe birth asphyxia and 30 healthy neonates matched for gestational and postnatal age were studied (**Fig. 1**). The data collected was entered in statistical software (SPSS® version 17.0), and standard statistical tests were applied. The continuous data were analyzed by analysis of variance in the normal distribution. Chi-square test or Fisher's exact test was used for categorical variables. The results will be considered significant at 5% level of significance ($p < 0.05$). Receiver operating characteristics (ROC) [10] was used to evaluate the diagnostic performance of renal Doppler.

Results

The study flow is depicted in **Fig. 1**. The demographic details of both groups are depicted in **Tab. 1**. There were no baseline differences between the two groups, except for mode of delivery. Thirteen out of 30 (43%) babies with severe birth asphyxia developed AKI. 31% had oliguric, and 69% had non-oliguric renal failure. Twelve out of the total 30 cases had hypoxic ischemic encephalopathy stage II or more as defined by Sarnat and Sarnat. This is 40% of the total severe birth asphyxia cases.

The comparison of the renal blood flow parameters between asphyxiated infants with AKI and asphyxiated infants without AKI revealed that on day 1 the PSV was significantly lower in those with AKI. However, this significance did not persist on day 3. Also, neither EDV nor RI was different between either of these groups (**Tab. 2**).

When a comparison was made between asphyxiated babies who developed AKI with healthy controls it was found that the EDV was

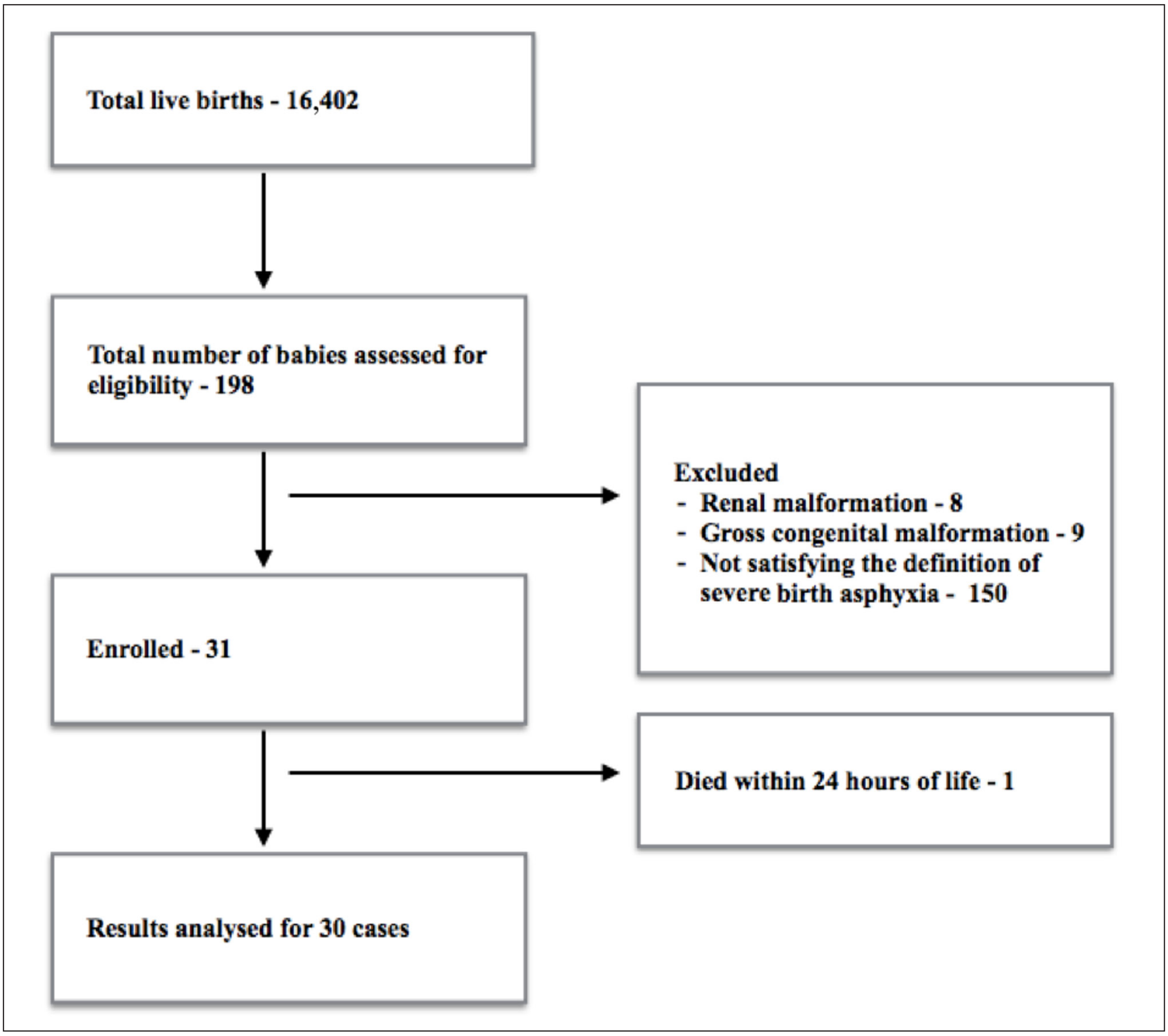

Figure 1. Study flow.

Table 1. Demographic details of cases and controls.

Demographic detail		Cases (n = 30)	Control (n = 30)	p-value
Gestational age (weeks)		36 ± 4	36 ± 4	0.50
Birth weight (grams)		2,300 ± 760	2,200 ± 686	0.31
SGA		8	7	0.40
AGA		22	23	
Sex	**Male**	17	16	0.40
	Female	13	14	
Mode of delivery	**Vaginal**	16	22	**0.04**
	LSCS	14	8	

SGA: small for gestational age; AGA: appropriate for gestational age; LSCS: lower segment Cesarean section.

Table 2. Renal blood flow parameters in asphyxiated babies with acute kidney injury (AKI) compared with that of asphyxiated infants without AKI.

Renal blood flow parameter	Day of life	Asphyxiated infants with AKI (n = 13)	Asphyxiated infants without AKI (n = 17)	p-value
PSV, cm/second	1	21.3 ± 7.2	25.7 ± 6.0	**0.039**
	3	24.3 ± 8.4	27.4 ± 5.22	0.124
EDV, cm/second	1	4.6 ± 0.9	5.4 ± 2.1	0.095
	3	4.7 ± 2.3	6.2 ± 2.2	0.059
RI, cm/second	1	0.76 ± 0.10	0.76 ± 0.09	0.429
	3	0.80 ± 0.11	0.77 ± 0.08	0.210

AKI: acute kidney injury; PSV: peak systolic velocity; EDV: end diastolic velocity; RI: resistive index.

significantly low in the asphyxiated babies with AKI compared with that of healthy controls both on day 1 and day 3 (**Fig. 2**).

The ROC curves were obtained for all the renal blood flow parameters on day 1 and day 3 to evaluate the diagnostic utility of renal Doppler ultrasonography in predicting acute renal failure in severe birth asphyxia. The area under the curve (AUC) was not significant for any of the parameters either on day 1 or day 3. The ROC curve and the AUC for day 1 renal blood flow parameters are shown in **Fig. 3**.

Discussion

The incidence of AKI was 43% in our study. AKI incidence in birth asphyxia in other studies was anywhere between 11-61% [11-16]. Two studies from the other parts of the world had quoted the incidence of AKI in babies with asphyxia to be 11.7% and 17.2%, respectively [13, 15]. This is much lower than the incidence in our study. The possible reasons could be the fact that these two studies had used a different definition for birth asphyxia and also that they had enrolled only neonates of term gestation. Also, the criteria to define AKI were different in these two studies from the criteria used in our study. The most recent multicentric AWAKEN study has reported an AKI incidence of 30% [17]. However, it is to be noted that the neonates with different disease conditions were enrolled in this study and the incidence of AKI in asphyxiated neonates was not specified.

The comparison of the renal blood flow parameters between asphyxiated infants with AKI and asphyxiated infants without AKI revealed that on day 1 the PSV was significantly lower in those with AKI. The possible explanation might be that, in those babies with asphyxia who end up with AKI, the renal blood flow might be decreased because of the diving reflex. However, why PSV alone is affected and not EDV and RI has to be studied further. Also, these significant changes did not remain on day 3, when the PSV was similar in both the groups. The presence of decreased renal blood flow on day 1 would have already resulted in renal insult with the baby developing AKI in the coming days. Similar findings were reported by Luciano et al. [18]. However, in their study, a significant difference was found not only in PSV, but also in EDV and RI, between asphyxiated babies with no AKI and asphyxiated babies who developed AKI.

Comparing asphyxiated babies who developed AKI with healthy controls it was found that the

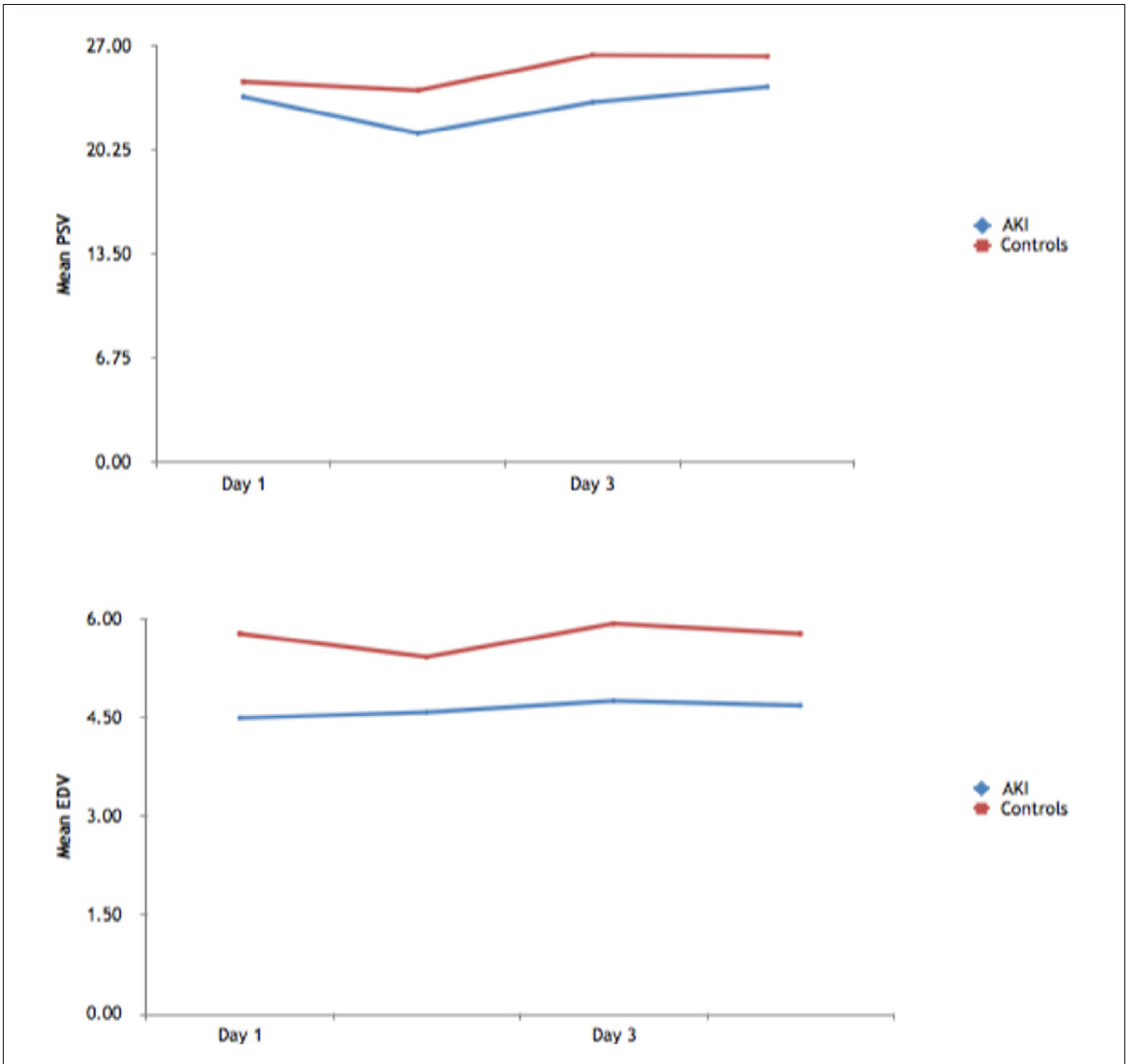

Figure 2. Renal blood flow parameters in asphyxiated babies with acute kidney injury (AKI) compared with that of healthy controls.
AKI: acute kidney injury; PSV: peak systolic velocity; EDV: end diastolic velocity.

EDV was significantly low in the asphyxiated babies with AKI both on day 1 and day 3. There was a trend towards a decreased PSV in the asphyxiated babies with AKI compared with healthy controls. However, the study by Luciano et al. had shown a different result: they had found a significant difference in PSV, EDV, and RI between the asphyxiated babies who developed AKI and normal healthy controls. The findings of their study and our study are compared in **Tab. 3**.

The ROC curves were obtained for all the renal blood flow parameters on day 1 and day 3 to calculate the sensitivity and specificity of the renal Doppler ultrasonography in predicting acute renal failure in severe birth asphyxia. The AUC was not significant for any of the parameters either on day 1 or day 3. This is contrary to the study by Luciano et al. were they had obtained sensitivity and specificity of 100% and 63%, respectively, for renal Doppler to predict AKI in birth asphyxia babies.

This study had significant differences with our study. These differences are presented below.

1. Gestational age and birth weight – The mean gestational age and birth weight in Luciano et al. study [1] was higher compared with that of our study. They had predominantly enrolled term babies. Gestational age of < 33 weeks was an exclusion criterion in their study. Whereas in

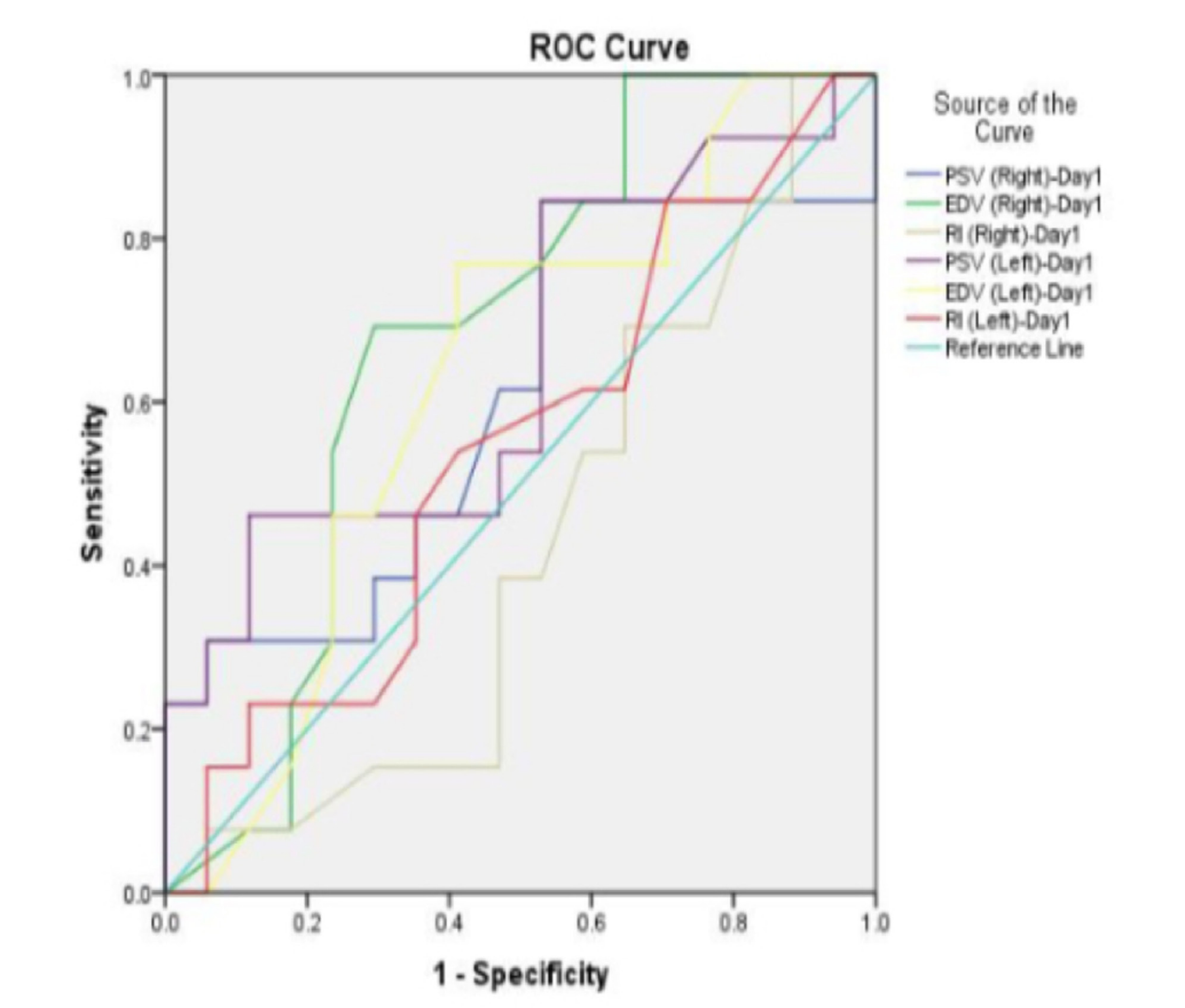

Figure 3. ROC curve for day 1 renal blood flow parameters.
ROC: receiver operating characteristics; PSV: peak systolic velocity; EDV: end diastolic velocity; RI: resistive index.

Table 3. Renal blood flow parameter between asphyxiated babies who developed acute kidney injury (AKI) and healthy controls.

Renal blood flow parameter	Our study			Luciano et al. [18]		
	Asphyxiated infants with AKI (n = 13)	Healthy controls (n = 30)	p-value	Asphyxiated infants with AKI (n = 7)	Healthy controls (n = 25)	p-value
PSV (± SD), cm/second	21.3 ± 7.2	24.7 ± 6.3	0.339	23 ± 2	48 ± 8	**< 0.001**
EDV (± SD), cm/second	4.6 ± 0.9	5.8 ± 1.7	**0.010**	5 ± 1	10 ± 3	**< 0.001**
RI (± SD), cm/second	0.76 ± 0.10	0.76 ± 0.06	0.134	0.79 ± 0.09	0.78 ± 0.04	**< 0.01**

AKI: acute kidney injury; PSV: peak systolic velocity; EDV: end diastolic velocity; RI: resistive index.

our study, 4 babies were extremely premature (< 29 weeks gestational age) and 2 babies were moderate preterms (29-33 weeks).

2. Small for gestational age (SGA) – Luciano et al. study had excluded SGA babies from their study. In our study about 30% of the enrolled subjects were SGA. SGA babies are known to have decreased renal blood flow. Maybe this is the reason why Luciano et al. had obtained a higher blood flow velocities in healthy controls

compared with the renal blood flow parameters of healthy controls in our study.

3. Respiratory support requirement – The controls in our study had required respiratory support, whereas none of the controls in Luciano et al. study had required respiratory support. This might be another reason for decreased renal blood flow parameters in the healthy controls in our study compared to that in Luciano et al. study.
4. Enrolment criteria – In our study, both cord pH and Apgar were used to define birth asphyxia. However, in Luciano et al. study cord pH was not taken as a criterion. Thus there were significant differences between the cases with birth asphyxia enrolled in our study and those in Luciano et al. study.

Even though there are some differences between our study and Luciano et al. study, the overall findings suggest that renal blood flow parameters are decreased in babies with asphyxia who later develop AKI. Since there is a paucity of normative data for renal blood flow in normal healthy neonates, it will be difficult to define what is low.

There are some significant strengths for our study. This is one of the few studies that have been done to date on renal Doppler ultrasonography in asphyxiated neonates from around the globe. No study has been done to date from the Indian subcontinent. To define severe birth asphyxia, both the Apgar score and the cord blood gas parameters were taken. Many of the studies have taken Apgar alone as a parameter for diagnosing severe birth asphyxia, and this would overestimate severe birth asphyxia, especially in preterm neonates.

There are some limitations to our study. This was only a prospective cohort study. The sample size was small with 30 neonates with severe birth asphyxia and 30 healthy neonates well matched for gestational age. Certain babies in the control group had received CPAP support for respiratory distress, which could itself affect the renal blood flow. The effect of other comorbidities such as respiratory support requirement, anemia, shock and polycythemia on the renal blood flow were not separately analyzed in the neonates with asphyxia. The gold standard used was serum creatinine whereas newer markers such as Cystatin C, Neutrophil-Gelatinase-Associated-Lipocalin (NGAL) and osteopontin are increasingly used to define AKI in perinatal asphyxia in recent times [19, 20].

Key messages

This study indicates that renal Doppler might only have a doubtful role in predicting AKI in perinatal asphyxia and further studies with large sample sizes are indicated in this aspect.

Declaration of interest

The Authors declare that there is no conflict of interest.

References

1. Wall SN, Lee AC, Niermeyer S. Neonatal resuscitation in low-resource settings: what, who, and how to overcome challenges to scale up? Int J Gynecol Obstet. 2009;107:S47-64.
2. Liu L, Oza S, Hogan D. Global, regional, and national causes of child mortality in 2000-13, with projections to inform post-2015 priorities: an updated systematic analysis. Lancet. 2015;385(9966): 430-40.
3. Aggarwal A, Kumar P, Chowdhary G, Majumdar S, Narang A. Evaluation of Renal Functions in Asphyxiated Newborns. J Trop Pediatr. 2005;51(5):295-9.
4. Miles RD, Menke JA, Bashiru M, Colliver JA. Relationship of five Doppler measures with the flow in an in vitro model and clinical findings in newborn infants. J Ultrasound Med. 1987;6:599-602.
5. Sonnesson SE, Herin P. Intracranial arterial blood flow velocity and brain blood flow during hypocarbia and hypercarbia in newborn lambs: a validation of range-gated Doppler ultrasound flow velocity. Pediatr Res. 1988;24:423-6.
6. Raju TN. Cerebral Doppler studies in the fetus and newborn infant. J Pediatr. 1991;118:621.
7. Gouyon JB, Guignard JP. Management of acute renal failure in newborns. Pediatr Nephrol. 2000;14:1037-44.
8. Khwaja A. KDIGO clinical practice guidelines for acute kidney injury. Nephron Clin Pract. 2012;120:c179-84.
9. Aggarwal R, Deorari AK, Paul VK; WHO Collaborating Centre for training and research in newborn. AIIMS Protocols in Neonatology 2014. Delhi: CBS Publishers, 2014. Available at: http://www.newbornwhocc.org/2014_pdf/Acute%20renal%20failure%202014.pdf, last access: 21 October 2018.
10. DeLong ER, DeLong DM, Clarke-Pearson DL. Comparing the areas under two or more correlated receiver operating characteristic curves: a nonparametric approach. Biometrics. 1988;44:837-45.
11. Gupta BD, Sharma P, Bagla J, Parakh M, Soni JP. Renal Failure in Asphyxiated Neonates. Indian Pediatr. 2005;42:928-34.
12. Aggarwal A, Kumar P, Chowdhary G, Majumdar S, Narang A. Evaluation of Renal Functions in Asphyxiated Newborns. J Trop Pediatr. 2005;51(5):295-9.
13. Nouri S, Mahdhaoui N, Beizig S, Zakhama R, Salem N, Ben Dhafer S. Methlouthi J, Seboui H. Acute renal failure in full-term neonates with perinatal asphyxia. Prospective study of 87 cases. Arch Pediatr. 2008;15(3):229-35.

14. Bhatnagar A, Bairwa AL, Meena KC. Incidence of Acute Kidney Injury in Perinatal Asphyxia and its Correlation with Hypoxic Ischemic Encephalopathy (HIE) Staging. Indian J Res. 2014;3(3):12-3.
15. Alaro D, Bashir A, Musoke R, Wanaiana L. Prevalence and outcomes of acute kidney injury in term neonates with perinatal asphyxia. Afr Health Sci. 2014;14(3):682-8.
16. Gopal G. Acute Kidney Injury (AKI) in perinatal asphyxia, Indian J Pharm Biol Res. 2014;2(2):60-5.
17. Jetton JG, Boohaker LJ, Sethi SK, Wazir S, Rohatgi S, Soranno DE, Chishti AS, Woroniecki R, Mammen C, Swanson JR, Sridhar S, Wong CS, Kupferman JC, Griffin RL, Askenazi DJ; Neonatal Kidney Collaborative (NKC). Incidence and outcomes of neonatal acute kidney injury (AWAKEN): a multicentre, multinational, observational cohort study. Lancet Child Adolesc Health. 2017;1(3):184-94.
18. Luciano R, Gallini F, Romagnoli C, Papacci P, Tortorolo G. Doppler evaluation of renal blood flow velocity as a predictive index of acute renal failure in perinatal asphyxia. Eur J Pediatr. 1998;157:656-60.
19. Askenazi D, Koralkar R, Hundley H, Montesanti A, Parwar P, Sonjara S, Ambalavanan N. Urine Biomarkers Predict Acute Kidney Injury in Newborns. J Pediatr. 2012;161(2):270-5.
20. Sweetman DU, Onwuneme C, Watson WR, O'Neill A, Murphy JF, Molloy EJ. Renal Function and Novel Urinary Biomarkers In Infants with Neonatal Encephalopathy. Acta Paediatr. 2016;105(11):e513-9.