

Original Article

Comparison of transcranial ultrasound and cranial MRI in evaluations of brain injuries from neonatal asphyxia

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Abstract: Full-term infants with early-stage brain injuries from asphyxia were examined with two-dimensional ultrasound and color Doppler to assess the use of ultrasound in evaluating early brain injuries after neonatal asphyxia. The sonographic features of ultrasound and color Doppler were compared to those of magnetic resonance imaging (MRI). Ultrasound was used to monitor the brain parenchyma, lateral ventricles, and cerebral hemodynamics in the asphyxia group and full-term control group 24, 48, and 72 h after birth. MRI and diffusion-weight imaging (DWI) were performed within 72 h. Cerebral edema changes were most obvious with ultrasound within 48 h of asphyxia, while the cerebral hemodynamic changes were most obvious within 24 h. These results suggested that ultrasound detected early cerebral edema better than MRI did.

Keywords: Ultrasound, neonate, asphyxia, brain injury, cerebral edema, MRI

Introduction

Neonatal asphyxia is an important cause of neonatal mortality and neurodevelopmental damage [1]. About four million neonatal deaths are reported worldwide each year, 1/4 of which are caused by asphyxia; moreover, 1-2% of living full-term infants develop hypoxic-ischemic encephalopathy (HIE) after asphyxia [2]. Approximately 7-10% of Chinese newborns suffer from asphyxia each year, and about 1/3 of these newborns die. Many of the surviving children develop severe neurological sequelae, such as cerebral palsy, intellectual impairments, and epilepsy. Therefore, the early detection and evaluation of postasphyctic brain injury, as well as the accurate assessment of prognosis, have been a focus of neonatology physicians [3]. Cranial ultrasound, which has developed rapidly since the 1980s, is one of the three main types of imaging technologies, together with Computed Tomography and Magnetic Resonance Imaging (MRI), used in the study of the neonatal central nervous system. The advantages and disadvantages of the use of these three technologies in the diagnosis of neonatal brain diseases have been

repeatedly demonstrated and compared [4, 5]. Conventional MRI (T1- and T2-weighted images), which is used most in clinics, clearly shows the anatomical structures of the brain, but it is not effective in the early detection of cerebral edema or cerebral white matter lesions, which results in significant delays in diagnosis [6]. Diffusion-weighted imaging (DWI) can reveal early HIE lesions within a few hours of the injury, which is earlier than MRI. However, DWI has a number of limitations, such as false negative results, underestimations of the full scope of the injury, and false normalization phenomena [7]. In contrast, two-dimensional (2D) ultrasound provides good images of the lateral ventricles and permits easy and accurate measurements [8]. Color Doppler ultrasound can monitor dynamic cerebral hemodynamics for assessing disease outcome and prognosis [9]. Because our hospital has recently started using cranial ultrasound technology, we set out to examine it, especially with respect to its potential role in the diagnosis and prognosis of patients with brain damage from neonatal asphyxia, its advantages compared with MRI, and its suitability for routine applications. This study focused on the imaging possibilities and

clinical significance of the use of 2D and color Doppler ultrasound for assessing patients in the early stages of brain injury after asphyxia. The ultrasound results were compared with those obtained with MRI and DWI. We aimed to provide a basis for determining the best choice among the imaging methods for evaluating patients with early neonatal asphyxia and determining their diagnoses and prognoses.

Methods

Subjects

The study subjects were divided into an asphyxia group and control group. The inclusion criteria were as follows. 1) For the asphyxia group, 30 asphyctic full-term neonates from Anhui Provincial Hospital who were treated from March 2011 to May 2012 were selected. The study protocol and investigations were explained to the parents, and informed written consents were obtained. Their gestational age was (mean \pm standard deviation) 39.9 ± 0.98 (range, 37.8-41.6) weeks, and their birth weight was $3,376 \pm 377$ g. The group included 19 males and 11 females. The patients had Apgar scores of 5 or less points or they had suffered from severe fetal distress (fetal heart rate < 100 beats/min for > 5 min). If the Apgar scores of the neonates were 3 or less points after 5 min, they were considered to have severe asphyxia. 2) For the control group, 20 neonates with normal full-term deliveries in the obstetric department during the same period were admitted into the normal newborn nursery for postuterine-incision delivery observations. Conventional cranial B ultrasound screening was performed. The parents gave informed written consents and agreed to these investigations. These control subjects did not have any histories of asphyxia or fetal distress. Their gestational age was 38.9 ± 1.23 (range, 37.6-41.0) weeks, and their birth weight was $3,223 \pm 442$ g. The group included 13 males and 7 females, and their Apgar scores were 9 or more points. The mothers of the infants in both the asphyxia and control groups had no birth trauma, infection, congenital heart disease, premature rupture of fetal membranes, diabetes, hypertension, cholestasis, or other diseases. The two groups did not differ significantly in gestational age, birth weight, or sex ratio ($P < 0.05$). This study was conducted in accordance with the

declaration of Helsinki. This study was conducted with approval from the Ethics Committee of Anhui Medical University. Written informed consent was obtained from all participants' guardians.

Routine coronal and sagittal section examinations conducted with ultrasound

Each neonate was placed in the supine position. When the infant was in a quiet state, a portable ultrasound system (probe frequency, 5.0 MHz; SonoSite, Inc., Bothell, WA, USA) was used to perform routine coronal and sagittal examinations through the anterior fontanelle. The echo patterns of the brain parenchyma, the shapes of the bilateral ventricles, and the widths of the bodies of the ventricles were determined for the two groups 24, 48, and 72 h after birth.

Color Doppler ultrasound was performed by using the anterior fontanelle as the acoustic window, and the peak systolic flow velocity (PSFV), end diastolic flow velocity (EDFV), and resistance index (RI) of the bilateral anterior cerebral arteries (ACA) and middle cerebral arteries (MCA) were determined for the two groups 24, 48, and 72 h after birth. Each measurement that included waves with a consistent shape was recorded at least three times in order to determine an average value. All of the original images and data were recorded.

MRI and DWI examinations

Within 72 h, 28 of the 30 cases in the asphyxia group were subjected to routine cranial MRI and DWI (Magnetom Trio 3.0T MRI, Siemens AG, Munich, Germany). Of the other two cases in the asphyxia group, one exhibited unstable vital signs and required normal-frequency mechanical ventilation, and the other exhibited a frequent minor twitch during the 72 h after asphyxia. These two cases were not subjected to cranial MRI.

Statistical analysis

The SPSS for Windows 16.0 statistical software (IBM Corporation, Armonk, NY, USA) was used for the analysis. The measurement data were expressed as mean \pm standard deviation. The measured values of each group and the values for the same group at different time points

Table 1. Ventricular lateral body width in 2 groups ($\bar{x} \pm s$)

Groups	Cases	Time (h)	Non-displaying rate (%)	Ventricular lateral body width (mm)	
				Left	Right
Asphyxia	30	24	65* (39/60)	0.64±0.76	0.63±0.88
Control	20	24	23 (9/40)	1.08±0.72	1.02±0.67
Asphyxia	30	48	58*# (35/60)	1.15±1.04	1.09±1.14
Control	20	48	8 (3/40)	1.65±1.76	1.67±2.08
Asphyxia	30	72	22# (13/60)	1.53±1.00	1.49±1.22
Control	20	72	5 (2/40)	1.69±0.97	1.72±1.32

Note: Comparison with control group at the same time point $P < 0.05$; * $P > 0.05$; # $P < 0.05$.

were analyzed with χ^2 tests and t -tests. P values less than 0.05 were considered statistically significant. Sensitivity and specificity were calculated with the following equations: Sensitivity = true-positive patients/(true-positive patients + false-positive patients) \times 100%; specificity = true-negative patients/(true-negative patients + false-negative patients) \times 100%.

Results

Two-dimensional ultrasound performance and measurement data

Twenty-four h after birth, 27 (90%) of the 30 cases in the asphyxia group displayed a wide range of patterns of enhanced brain parenchymal echo, and the echo strength was equal to or slightly lower than that of the choroid plexus. The brain structures appeared fuzzy with shallow sulci and narrow or undetected ventricles. The body of the left lateral ventricle was undetected or slit-shaped in 19 cases, and the right lateral ventricle exhibited abnormalities in 20 cases. The percentage of asphyxia cases with undetected ventricles was 65% (39/60) compared with 23% in the control group at the same time point, and this difference was statistically significant ($P < 0.05$), with a sensitivity and specificity for diagnosing cerebral edema by ultrasound within 24 h of 90% and 75%, respectively. Lateral intraventricular hemorrhages were seen in six cases, including three with subependymal hemorrhages, but these observations were not associated with ventricular dilatation. One case exhibited an intracranial hemorrhage. Forty-eight hours after birth, 24 cases (80%) showed diffuse enhancement of the parenchymal echo pattern, which was

especially significant around the ventricle. The percentage of cases with undetected lateral ventricular bodies was 58% (35/60) in the asphyxia group compared with 8% in the control group at the same time point. This difference was statistically significant ($P < 0.05$). However, the differences in the percentages at 48 h did not significantly differ from that at 24 h, and the sensitivity and specificity for diagnosing cerebral edema with ultrasound within 48 h were 80% and 90%, respectively. Seventy-two h after birth, 17 cases (57%) still exhibited an enhanced pattern of parenchymal echo.

The periventricular triangular region was more obvious, and the brain structures were more clear. The percentage of cases with undetected lateral ventricles was 22% (13/60) in the asphyxia group compared with 5% in the control group. This difference was statistically significant ($P < 0.05$). In addition, the differences in the 24-h and 48-h time points were statistically significant ($P < 0.05$). Among the six cases with intraventricular hemorrhages, two exhibited ventricular dilatation, which was thought to mainly be due to expansion of the posterior horn. The sensitivity and specificity of diagnosing cerebral edema by ultrasound within 72 h were 56.67% and 95%, respectively. The data for the dynamic changes to the lateral ventricles and the measurements that were made at 72 h for the two groups are shown in **Table 1**. **Figure 1A-C** shows the 2D ultrasounds that were performed 24, 48, and 72 h after the asphyxia.

Color doppler ultrasound manifestations and blood parameters

The hemodynamic parameters of the left and right ACA and MCA did not differ significantly for the two groups at the same time points. Thus, the data from the left side are presented as an example.

All 120 ACA and MCA vessels in the asphyxia group were examined 24 h after birth. The vascular spectra of 80 vessels (67%) showed low velocity and high impedance ($RI > 0.75$). The PSFV and EDFV were decreased, with greater significance for the EDFV difference, and the RI was increased. No vessel exhibited spectra with a single systolic peak or diastolic flow reversal. Another eight vessels (7%) showed

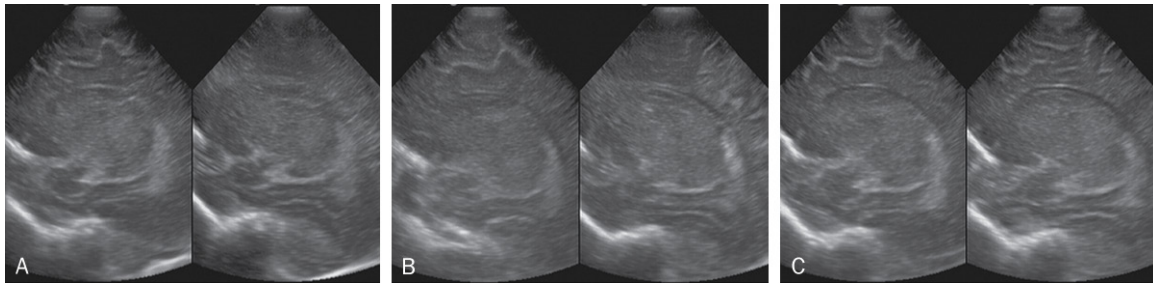


Figure 1. 2D color ultrasound after delivery. A: 24 h after delivery; B: 48 h after delivery; C: 72 h after delivery.

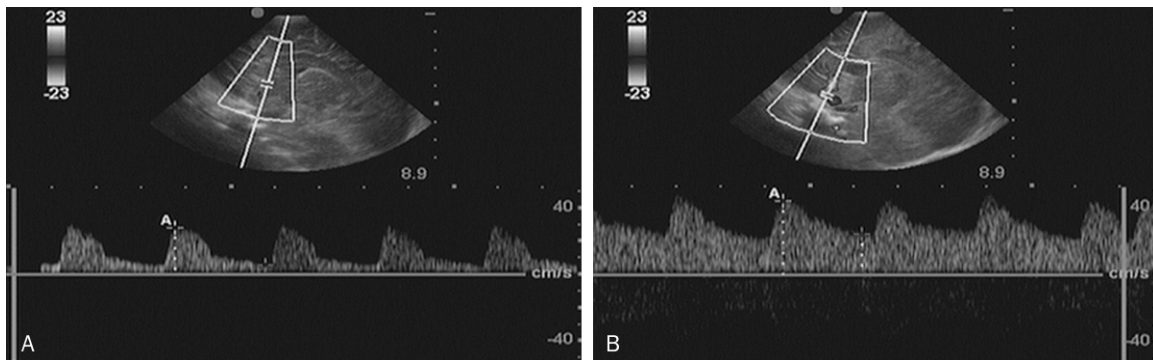


Figure 2. A: Low-speed high-resistance; B: High-speed low-resistance.

high-velocity and low-resistance spectra ($RI < 0.55$), in which the PSFV and EDFV were increased, while the RI was decreased. The infant with severe asphyxia who twitched continuously after birth and later died when treatment was discontinued on the fourth day exhibited four vessels with RIs less than 0.50. A patient with severe HIE who became comatose within 1 week of birth exhibited four vessels with RIs over 0.90. A low-velocity and high-impedance Doppler spectrum is shown in **Figure 2A**, and a high-velocity and low-resistance Doppler spectrum is shown in **Figure 2B**.

The postbirth cerebral hemodynamics of the asphyxia group was significantly changed at 24 h compared to those of the control group. The PSFV, EDFV, and RI values of the ACA and MCA at 48 h in the asphyxia group differed significantly compared with the values of the same vessels at 24 h, but the values at 72 h did not significantly differ compared with those at 48 h.

The PSFV, EDFV, and RI values of the ACA and MCA 24 h after birth differed significantly between the two groups. From 48 to 72 h, the PSFV and EDFV values rebounded, the RI

declined, and the hypoxic group no longer differed significantly compared with the control group ($P > 0.05$). The blood flow parameters of the left ACA and MCA in the two groups are compared in **Table 2**.

MRI and DWI performance

Routine cranial MRI and DWI examinations were performed on the 28 cases in the asphyxia group (the two cases with severely unstable vital signs were not examined). Among these cases, one exhibited multiple small, patchy, and short T1 and T2 signals on the MRI scans, and DWI detected diffuse or localized signal enhancement (corrected χ^2 test, $P < 0.1$) in seven cases; parenchymal hemorrhage in four cases, including one case of intraventricular hemorrhage; three cases of subarachnoid hemorrhage; and no ventricular dilatation (**Figure 3A, 3B**). The sensitivity and specificity of cranial MRI for diagnosing cerebral edema were 25% and 100%, respectively.

Discussion

Brain edema is a pathological change that is characteristically observed after asphyxia [10],

Table 2. Blood flow parameters of left cerebral artery in 2 groups (cm/s, $\bar{x} \pm s$)

Vessel	Group	Cases	Time (h)	PSFV	EDFV	RI
ACA	Asphyxia	30	24	25.70±3.92 ^{*,#}	8.37±2.27 ^{*,#}	0.71±0.11 ^{*,#}
	Control	20	24	32.50±2.82 [*]	12.62±2.24 [*]	0.62±0.06 [*]
	Asphyxia	30	48	32.08±3.77 [#]	12.01±3.04 [#]	0.63±0.10 [#]
	Control	20	48	33.29±2.31	12.83±1.90	0.63±0.05
	Asphyxia	30	72	33.24±3.17	12.85±2.55	0.62±0.09
	Control	20	72	34.80±2.12	13.17±1.79	0.63±0.08
MCA	Asphyxia	30	24	34.20±3.71 ^{*,#}	9.08±4.96 ^{*,#}	0.73±0.10 ^{*,#}
	Control	20	24	42.71±3.24 [*]	14.91±2.99 [*]	0.65±0.07 [*]
	Asphyxia	30	48	42.38±4.07 [#]	14.20±5.44 [#]	0.67±0.11 [#]
	Control	20	48	45.86±3.14	15.59±3.53	0.65±0.08
	Asphyxia	30	72	43.30±4.03	15.98±5.24	0.63±0.10
	Control	20	72	44.41±4.27	16.28±3.70	0.64±0.12

Note: Comparison of PSFV, EDFV and RI of ACA and MCA in both groups at the 24th hour, ^{*}*P* < 0.05; comparison of PSFV, EDFV and RI in asphyxia group between the post-birth 48th and 24th hour, [#]*P* < 0.05.

and the main ultrasound manifestation of brain edema is diffuse parenchymal echo enhancement. More intense patterns of parenchymal echo indicate more severe neuronal damage. With brain edema, the intracranial structures appear fuzzy with shallow sulci and narrowed or undetected ventricles [11]. The extent and time required for the cerebral edema to subside are closely related to the neonatal prognosis. The results of this study indicated that the changes in the parenchymal echo pattern and ventricles that were induced by cerebral edema were most obvious 48 h after asphyxia and partly restored at 72 h, which confirmed that the cerebral edema peaked at 48 h. In addition, this study found that a significant difference in the percentage of cases with undetected lateral ventricles between the two groups was still found at 72 h. Thus, these findings suggested that the brain edema improved after 48 h, but it still had not subsided even after 72 h. Because the neonatal fontanelle and cranial sutures are not closed, the increased intracranial pressure that is caused by cerebral edema is far less obvious in infants than it is in adults, and the clinical manifestations of cerebral edema are atypical and easily overlooked. Therefore, early ultrasound examinations can determine the presence and extent of cerebral edema and allow observations of the dynamic outcome of the edema, which helps to determine the condition and prognosis of the patient. However, 2D ultrasound cannot clearly diag-

nose parasagittal damage or bleeding at the edge of the cranium. Quantitative and objective criteria for judging the severity of brain echo enhancements have not been established, and these subjective judgments can be affected by the condition of the instrument and the examiner's experience [12]. Therefore, the use of ultrasound has limitations when it is used to diagnose brain edema in the early stages after asphyxia.

Hemodynamic changes are involved in the major pathophysiological mechanisms that underlie postasphyxia

brain damage [13]. Many studies from China and other countries have used color Doppler ultrasound to monitor the hemodynamic changes that occur in the brain after asphyxia, but the results have been inconsistent. Ilves et al. [14] have found that infants with severe HIE exhibit increased blood flow velocities of cerebral artery blood and decreased RI values within 24 h of asphyxia, thus indicating high velocity and low resistance. Those authors suggested that hyperperfusion was the most important manifestation of brain injury in the early stages after asphyxia. Liu et al. [9] have suggested that the cerebral blood flow of HIE patients is disordered and that the RI can significantly increase or decrease within the first 24 h of asphyxia. Patients with severe HIE have RIs that are less than 0.50 or greater than 0.90, and brain death occurs when the RI is greater than 1.0. The current study showed that high-velocity/low-impedance or low-velocity/high-impedance cerebral hemodynamic changes were most obvious after 24 h, but the majority of patients (67%) showed the low-velocity/high-impedance changes with low cerebral blood perfusion. RI values over 0.75 or less than 0.55 indicate disorders with impaired autoregulation of cerebral blood flow. RI values greater than 0.90 or less than 0.50 indicate serious conditions, which is consistent with the findings of Liu et al. [9] The results of reports from China and other countries [9, 14-18], as well as the results of this study, suggest that cerebral per-

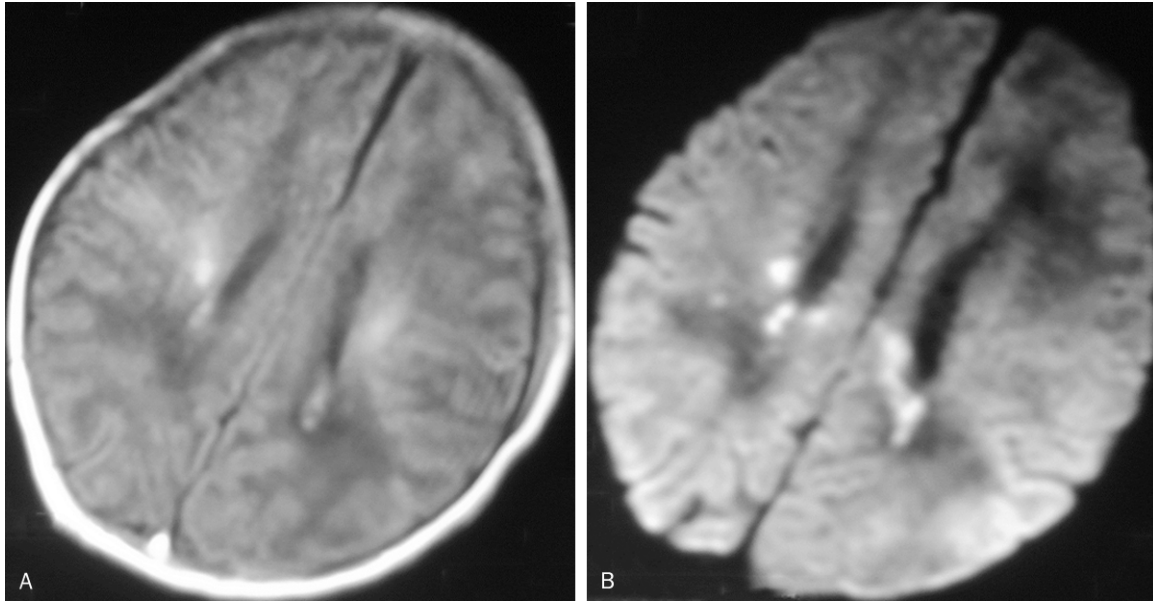


Figure 3. A: MRI; B: DWI.

fusion and RI changes after asphyxia are associated with the extent, duration, and length of the time until examination. The changes that occurred in cerebral blood flow immediately after birth were the most obvious and most dynamic.

Because Color Doppler ultrasound is simple and non-invasive and does not require the use of a contrast agent, it has become the preferred method for monitoring postasphyxia cerebral hemodynamics. However, this technique has a number of disadvantages. First, cerebral blood flow is susceptible to external factors that generate fluctuations, which make it difficult to obtain stable and reliable hemodynamic parameters. For example, the use of sedatives might affect cerebral blood flow and make it difficult to determine the real changes in blood flow in infants. Second, recent studies that have been conducted in China and other countries, including this study, have mostly monitored cerebral blood flow in vessels, such as the ACA, MCA, posterior cerebral artery, internal carotid artery, or basilar artery. No systematic studies have been conducted on the main arteries that supply blood to the white matter of the brain, such as Charcot's artery. Normally, the hemodynamic parameters do not exhibit obvious changes in the early stages or in mild asphyxia, and the monitoring of the branches of the aorta might be much more

informative. This would be a great subject for future research.

In this study, 28 cases were all subjected to cranial MRI and DWI examinations, and seven cases with signal abnormalities were found to meet the criteria for a diagnosis of cerebral edema with a sensitivity and specificity for diagnosing cerebral edema of 25% and 100%, respectively. In contrast, 27 of the 30 patients in the asphyxia group were diagnosed with cerebral edema with 2D ultrasound within 24 h of birth (sensitivity, 90%; specificity, 75%). Of these patients, 17 still showed evidence of cerebral edema after 72 h (sensitivity, 56.67%; specificity, 95%). The difference between the data collected with these two imaging methods was statistically significant, indicating that the sensitivity of 2D ultrasound for detecting brain edema in the early stages of asphyxia was higher than that of cranial MRI and DWI. Conventional MRI only revealed one case with abnormal signals, and DWI found seven cases with abnormal signals (corrected χ^2 test, $P < 0.1$), indicating that the detection of cerebral edema lesions in the early postasphyxia stage was better with DWI than with MRI. Of the six cases with lateral ventricular hemorrhages that were clearly diagnosed with 2D ultrasound, MRI and DWI only detected one. Thus, three cases with subependymal hemorrhages were missed. However, of the four cases with cerebral parenchymal hem-

orrhages that were detected with cranial MRI and DWI, only one was successfully diagnosed with 2D ultrasound. Thus, three cases with subarachnoid hemorrhages were missed by 2D ultrasound, further confirming that MRI and DWI have advantages in the detection of spotty hemorrhages in the cerebral parenchyma and subarachnoid hemorrhages compared with 2D ultrasound, while MRI and DWI have poor diagnostic sensitivity for intraventricular hemorrhages, especially subependymal hemorrhages [19]. At 72 h after asphyxia, 2D ultrasound diagnosed two cases with intraventricular hemorrhage with ventricular dilatation, while cranial MRI and DWI did not detect these abnormalities, indicating that MRI was less effective than 2D ultrasound for the observation and measurement of the ventricles. Because the asphyxia group had a very low positive rate, statistical analysis could not be performed. Cranial MRI and DWI are expensive, they require lengthy examination sessions, and the subjects need to be moved and tranquilized. Timely imaging examinations of severely affected children for clinical assessments would be difficult [20]. Thus, cranial ultrasound is much more suitable for the early diagnosis, dynamic monitoring, and assessments of the prognosis of infants with this disease.

The brain edema changes were most obvious within the first 48 h after asphyxia, and the 2D ultrasound demonstrated these well, thus making it the best choice for dynamic observations of the lateral ventricles. The cerebral hemodynamic changes were most obvious within the first 24 h after asphyxia, and these changes were closely related to the degree of brain damage. The RI, which can assist in the early diagnosis and severity determination of HIE, should be examined as an important indicator of the changes after asphyxia. MRI can more clearly detect lesions in the parasagittal region, posterior fossa, and outer edges of the brain that B-mode ultrasound cannot detect well. In addition, MRI accurately reflects the anatomical sites, extent, and pathological types of brain injuries after asphyxia, but it has obvious delays when making a diagnosis [21]. DWI can complement the positive features of MRI, and it plays an important role in the early diagnosis of postasphyxia brain damage. Although MRI and DWI have advantages over 2D ultrasound in the detection of spotty hemorrhages in the cere-

bral parenchyma and subarachnoid hemorrhages, their diagnostic use and repeatability for early lesions, such as brain edema, intraventricular hemorrhage, and ventricular dilatation, were less accurate than cerebral ultrasound. Thus, timely examinations would be limited by the constraints that are imposed by the illness. In clinical practice, the choice of imaging methods should be based on the above considerations.

Conclusions

The use of 2D ultrasound showed that the first 48 h after asphyxia was the peak time for cerebral edema. The RI was an important parameter of cerebral hemodynamics, and the changes in cerebral hemodynamics were most obvious 24 h after asphyxia. MRI was not more sensitive than cranial ultrasound in the detection of early lesions in cerebral edema, and the use of DWI for the detection of early postasphyxia cerebral edema was better than conventional MRI.

Disclosure of conflict of interest

None.

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