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Color Doppler blood flow indices of the superior mesenteric artery as an early predictor of necrotizing enterocolitis in preterm neonates

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Abstract: Background: Necrotizing enterocolitis is the most common sever gastrointestinal emergency that affects premature newborns. It is often has a rapid onset with few signs that can be used to predict its occurrence. Its rapid onset and progression to morbidity and mortality initiates the researchers for seeking early diagnostic tools helping in detection infants at risk for development of the disease, for whom early preventive measures could be targeted. Previous studies have shown that high resistance patterns of mesenteric arterial Doppler flow velocimetry are associated with a significantly reduced tolerance to enteral feeding. Moreover, groups of infants deemed to be at increased risk of necrotizing enterocolitis tended to have high resistance patterns of flow in the superior mesenteric artery. AIM: To evaluate the Doppler blood flow indices of the superior mesenteric artery (SMA) in pre-term neonates at risk for developing necrotizing enterocolitis (NEC). Materials and Methods: This prospective study included 52 preterm neonates, whose gestational age was less than 34 weeks. All of the neonates were subjected to clinical assessments, laboratory investigations and color Doppler flow evaluation of the SMA (including PSV, EDV, RI and PI) on the first day of life. Necrotizing enterocolitis was diagnosed and classified based on Bell's staging criteria with Walsh and Kliegman's modifications. Clinical management and diagnosis of NEC were performed blind to the Doppler results. Statistical analysis was performed using the Mann-Whitney U test, and *P*-values less than or equal to 0.05 were statistically significant. Receiver operating characteristic (ROC) curves were used to determine the optimal threshold values of PSV, EDV, RI and PI, using MedCalc software, version 12.7.8.0. Results: The study included 52 preterm neonates, whose gestational age was less than 34 weeks. Twelve neonates (23%) developed NEC and were designated as group I, and the remaining 40 neonates (77%) were designated as group II. The median birth weights in groups I and II were 1000 and 1870 g, respectively, with a statistically significant difference of $P < 0.05$. Doppler indices of the SMA, peak systolic velocity (88.9 ±17 and 53 ±8.5 cm/s), end diastolic velocity (18.75±11.3 and 14.9±5.6 cm/s), resistive index (0.78±0.09 and 0.67±0.1) and pulsatility index (1.53±0.73 and 0.67 ± 0.15) were higher in group I than in group II, with statistically significant differences. Conclusion: Preterm infants with high resistance patterns of blood flow velocity in the SMA on the first day of life were at increased risk for developing necrotizing enterocolitis.

Keywords: Color Doppler Ultrasonography, Superior Mesenteric Artery, Necrotizing Enterocolitis, Preterm Birth, Neonates

1. Introduction

Neonatal necrotizing enterocolitis (NEC) is the most common serious gastrointestinal disorder affecting preterm infants. [1] The incidence of NEC varies from center to center and from year to year within centers. There have been endemic and epidemic occurrences. In most centers, NEC occurs in 2-5% of all neonatal intensive care unit (NICU) admissions.[2] A multifactorial pathogenesis has been suggested, involving risk factors such as

gastrointestinal ischemia, enteral feeding and microorganisms, in combination with immaturity. Progress in the prevention of NEC has been limited by difficulties in clearly defining the condition and also in an inability to identify subsets of premature infants at greater risk for developing NEC.[3] The diagnosis of NEC is based on clinical criteria and radiographic findings. [4] Plain abdominal X-rays remain the standard imaging modality for diagnosing NEC. Ultrasonography has improved in its role in the diagnosis and follow-up of NEC. However, it is still not recognized that it can improve upon the information provided by plain abdominal X-rays and that it can affect the management of NEC. Plain abdominal radiography and the abdominal ultrasonography can both detect intramural gas and portal vein gases, as well as free intraperitoneal gas. The major advantages of ultrasonography over plain abdominal X-ray is that it can detect intraabdominal fluid and can also estimate the bowel wall thickness. Ultrasonography can also detect a nonviable bowel as it can detect marked thinning of the bowel wall and can assess bowel wall perfusion before the occurrence of perforation; additionally, this thinning is usually observed before the detection of pneumoperitoneum on plain abdominal X-rays. The mortality rate is higher after perforation; thus, earlier diagnosis of severely ischemic bowels loops before perforation could potentially improve morbidity and mortality due to NEC. [5-7] The superior mesenteric artery is the second major branch of the abdominal aorta, and it has its origin immediately below the celiac trunk in the ventral wall of the aorta. The SMA is the blood vessel predominantly supplying the small and large bowels. With advances in ultrasonographic technology, using color Doppler ultrasound to assess the blood flow parameters of the superior mesenteric artery (SMA), including peak systolic flow velocity (PSV), end diastolic flow velocity (EDV), mean flow velocity (MFV) and pulsatility index (PI), on the first day of life in preterm infants could be a useful non-invasive procedure for predicting those preterm infants that are at increased risk for developing NEC.[8].

2. Material and Methods

Research Ethics Committee approval and informed consent of the patients' parents were both obtained. The study included 52 preterm neonates delivered and admitted to the NICU from February 2011 to May 2013. The inclusion criterion was preterm birth at less than 34 weeks (gestational age). The exclusion criteria were the presence of congenital anomalies or proven sepsis. All of the patients were subjected to full clinical examinations, which included antenatal and natal histories with a special emphasis on risk factors for NEC, such as preeclampsia, diabetes, amnionitis, premature rupture of membranes, antenatal steroids and maternal infection. Laboratory investigations included complete blood count, Na, K, calcium, magnesium, random blood sugar, C-reactive protein, blood culture and arterial blood gases. Stool analysis for occult blood and stool culture for cases of NEC were performed. Radiologic investigations included plain chest X-ray chest for cardiorespiratory assessment and plain X-ray of the abdomen for cases with NEC. A color Doppler ultrasonographic study of the SMA was conducted on the first day of life.

2.1. Superior Mesenteric Artery Doppler Flow Velocimetry Technique

Real-time color Doppler ultrasound examination of the blood flow velocity in the SMA was performed during the first 24 hours of neonatal life, provided there was a period of cardiorespiratory stability (defined as mean blood pressure >30 mm Hg, continuous oxygen saturation monitoring at 90-95%, and/or the last blood gas revealing pH>7.25, PaCO2 of 35-45 mm Hg and PaO2 60-80 mm Hg). The scanning was performed using a color Doppler scanner (Voluson 730 Pro) from GE Healthcare (Milwaukee, WI, USA) equipped with a 7.5 to 12 MHz linear probe. Both gray scale and color Doppler ultrasonography exams were performed in all of the neonates. First, in real time, ultrasonography of the SMA was obtained in axial scan, and then the transducer was rotated to obtain a longitudinal scan of the SMA. The color box was applied to the SMA artery and aorta, the pulse repetition frequency was adjusted just below color aliasing, and the color flow toward the transducer was assigned a red color. The pulsed Doppler was applied, and the sample volume was adjusted just distal to the origin of the SMA. Corrections were made for the angle of insonation to 60 degrees in all of the examinations. From the recorded Doppler tracings, peak systolic velocity, end diastolic velocity, resistive index and pulsatility index were obtained by automatic tracing of the scanning machine over at least 5 consecutive cardiac cycles. Three measurements were recorded from each case, and the final measurements were the mean of these 3 readings.

The results of SMA Doppler flow indices were not disclosed to the attending neonatologist, so the clinical management of the cases, including the timing and volumes of feeding and the diagnosis of NEC and comorbidities, were performed blinded to the Doppler results.

Necrotizing enterocolitis was diagnosed and classified according to the Bell staging criteria and the modifications made by Walsh and Kliegman (1986).[9]

2.2. Statistical Analysis

Statistical analysis of variables was performed using the Mann-Whitney *U* test. Statistical significance was assumed at values of $P<0.05$. All of the statistical analyses were performed using the MiniTab software package, version 16.

Receiver operating characteristic (ROC) curves were used to determine the optimal threshold values of PSV, EDV, RI and PI, using the MedCalc software, version 12.7.8.0.

3. Results

This study was conducted on 52 preterm infants who were delivered and admitted to the NICU from February 2011 to May 2013. Their gestational ages ranged from 26 – 33 weeks, and their birth weights ranged from 870 g to 2290 g. Twenty-two were male, and thirty were female. The study demonstrated that 12 patients developed NEC (five of them had stage I NEC "suspected", 6 had stage II, and one had stage III with intestinal perforation) on a clinical basis. The 12 patients who had NEC were referred as group I, with the remaining 40 neonates referred to as group II.

No statistically significant differences were found regarding the sexes between group I and group II (P> 0.05). The gestational ages of the neonates in group I ranged between 26 and 31 weeks, while they ranged between 28 and 33 weeks in group II with no statistically significant difference (P> 0.05). The median birth weights in groups I and II were 1000 and 1870 g, which was statistically significant (P< 0.05; table 1).

Table 1. *Demographic distribution of the studied neonates.*

Demographic distribution	Group I N = 12	Group II N = 40	P-value
Male/female	5/7	17/23	> 0.05
Gestational age in weeks (median)	26 – 31 (28) weeks	28 – 33 (30) weeks	> 0.05
Birth weight in grams (median)	870 – 1340 (1000) g	980 – 2290 (1870) g	< 0.05

The median times to establish 50% feeding in group I and group II were 16 and 6 days, respectively with a statistically significant difference (P< 0.05), while the median times to establish full feeding were 25 and 10 days.

The Doppler indices of SMA included the peak systolic velocity (PSV), the end diastolic velocity (EDV), the resistive index (RI) and the pulsatility index (PI), and these values were statistically different between group I and group II (P-value < 0.05). The results of the comparisons of measurements between the groups and the ROC cutoff values to detect affected subjects are presented in (table 2).

Table 2. *Doppler flow indices in the SMA in group I and group II*

Indices	Group I N = 12	Group II N = 40	P-value	Cutoff cm/s	Sensitivity	Specificity
PSV Range Mean ±SD	60 – 112 cm/s 88.9 ±17 cm/s	39 - 78 cm/s 53±8.5 cm/s	< 0.05	> 76 cm/s	83.3%	97%
EDV Range Mean ±SD	5 – 34 cm/s 18.75±11.3 cm/s	4 – 33 cm/s 14.9±5.6 cm/s	< 0.05	> 20 cm/s	25%	82%
RI Range Mean ±SD	0.64 – 0.94 0.78 ± 0.09	0.37 – 0.91 0.67 ±0.1	< 0.05	> 0.76	58.3%	85%
PI Range Mean ±SD	0.98 – 2.8 1.53±0.73	0.63 – 0.90 0.67 ± 0.15	< 0.05	>0.9	100%	100%

4. Discussion

Necrotizing enterocolitis is an acquired condition of diffuse necrotic injury to the mucosal and submucosal layers of the bowel. It is the most serious gastrointestinal (GI) disorder that occurs during the neonatal period.[10]

Premature infants can experience vasoconstriction, hypotension and thrombosis, leading to decreased GI perfusion and GI mucosal injury.[11] Indwelling umbilical artery catheters (UACs) can decrease blood vessel diameters and flow, resulting in GI ischemia.[12] Decreased GI perfusion can start in utero and can be clinically silent, until the clinical symptoms of NEC appear.[13] In neonates, impairment of the blood supply to the bowel has been thought to play an important role in the causation of NEC, which is often fatal.[7]

Data have suggested that either abnormalities of the development of the splanchnic circulation in fetal life or vasoconstriction of the circulation in neonatal life plays a role in the etiology of NEC. This theory is consistent with current hypotheses of the pathophysiology of NEC, which suggest that mucosal ischemia is a key initiating event. Previous studies have shown that high resistance to flow in the SMA was associated with a delay in establishing feeding and those infants with risk factors for NEC tended to have higher resistance patterns of flow in the SMA. [8, 14]

In this study, twelve neonates (23%) developed NEC, which is a relatively high incidence of NEC and could be explained by most studied neonates who developed NEC having extremely low birth weights (<1000 g); this finding was in accordance with those of Kliegman et al.[15], who stated that among infants with very low birth weights (VLBW, <1500 g), the incidence might be as high as 15%, with a mortality rate of 10-30%.

In this study, blood flow indices (PSV, EDV, RI and PI) were higher in group I, which developed NEC, than in group II, which did not, with a statistically significant difference. This outcome could be explained by the infants who developed NEC (group I) having gut ischemia as a result of reductions in fetal aortic blood flow in response to uteroplacental insufficiency, thus producing fetal hypoxia and redistribution of blood flow toward the brain. The changes observed on the first day of life most likely represent persistence of these fetal redistribution patterns into postnatal life, as stated in the study by Campbell et al. [16]

In this study, the patterns of Doppler flow indices indicating increased resistance in the SMA were associated with an increased risk of NEC. This finding was in accordance with those of Murdoch et al.[14], who suggested that splanchnic flow was compromised immediately after birth in many infants who went on to develop NEC.

Doppler flow indices indicating increased resistance in the SMA, measured during the first 24 hours of life, have been associated with an increased risk of NEC in preterm neonates. This association could form the basis of biophysical risk scoring for NEC among extreme preterm neonates, which could, in turn, assist in making informed clinical management decisions, such as feeding regimens, in these neonates.

5. Limitations and Positive Features

We believe that one of this study's limitations was the relatively small number of necrotizing enterocolitis cases included; however, the ROC analysis and consideration of cutoff values, as well as adding the resistive index as a new value that was not mentioned in the previous studies, could facilitate future studies involving a larger number of NEC cases with more reliable cutoff values.

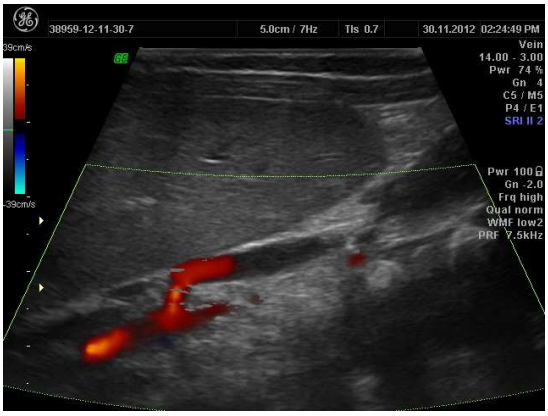

Figure 1. *Color Doppler examination shows the origin of the SMA from the aorta on the longitudinal plane*

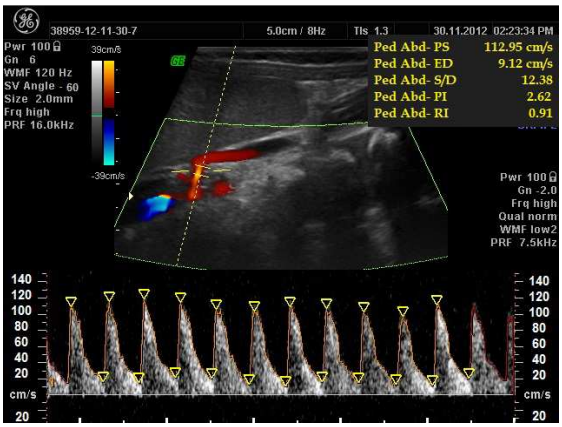

Figure 2. *Color Doppler examination of the SMA flow indices in a neonate aged 29 weeks who later developed NEC (PSV 112 cm/s, EDV 9 cm/s, RI 0.9, PI 2.6)*

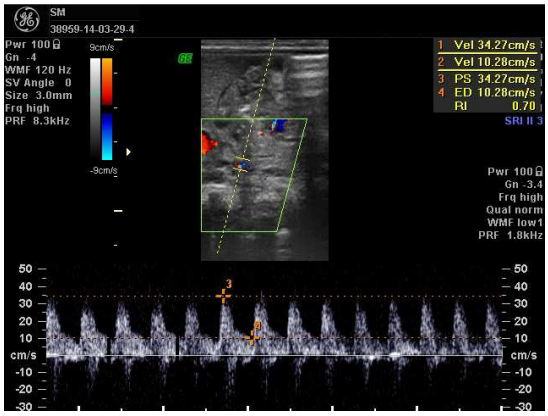

Figure 3. *Color Doppler examination of the SMA flow indices in a neonate aged 32 weeks who did not developed NEC (PSV 34 cm/s, EDV 10 cm/s, RI 0.7, PI .86)*

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