Cukurova Medical Journal
ÇUKUROVA ÜNİVERSİTESİ TIP FAKÜLTESİ

Cukurova Med J 2020;45(1):1-8
DOI: 10.17826/cumj.645596

ARAŞTIRMA / RESEARCH

Prognostic value of whole blood count parameters and echocardiographic findings in infants with hypoxic ischemic encephalopathy

Hipoksik iskemik ensefalopatili infantlarda tam kan sayımı parametreleri ve ekokardiyografi bulgularının prognostik değeri

Derya Karpuz[1], Yalçın Çelik[2], Derya Duman[3], Fatma Durak[4], Gülçin Bozlu[5], Dilek Giray[1], Baki Kara[5], Olgu Hallioglu[1]

[1]University of Mersin Faculty of Medicine, Department of Pediatrics, Division of Pediatric Cardiology, [2]Department of Pediatrics, Division of Neonatology, [5]Department of Pediatrics,Mersin, Turkey
[3]Hatay City Hospital, Division of Pediatric Cardiology, Hatay, Turkey
[4]Kayseri City Hospital, Department of Pediatrics, Kayseri, Turkey

Cukurova Medical Journal 2020;45(1):1-8.

Abstract

Purpose: The aim of this study was to investigate the prognostic value of complete blood count parameters, presence of pulmonary hypertension (PH) and valve failure in newborns with hypoxic ischemic encephalopathy (HIE).

Materials and Methods: 115 term newborns with Sarnat Stage 2 and 3 with HIE and 90 healthy newborns were included in this retrospective study. Echocardiographic examination, red blood cell distribution width (RDW), platelet distribution width (PDW), and C-reactive protein (CRP) values at the first six hours and at 72 hours after the cooling treatment were compared with controls.

Results: The estimated mean systolic and diastolic pulmonary arterial pressures (PAP) were higher and ejection fraction values were lower in infants with stage 3 HIE than with stage 2. The mean RDW, PDW and CRP levels at the first six and after 72 hours were significantly higher in infants with HIE when compared with the control group, and these parameters were significantly increased in the stage 3 group. **Conclusion:** The degree of PH and presence of valvular insufficiency are important parameters in determining prognosis in HIE. Also, simple blood tests such as RDW and CRP and the echocardiographic evaluation are found to be correlated with hospitalization period and mortality and may be a guide in prognosis.

Key words:. Echocardiography, hypoxic-ischemic encephalopathy, pulmonary hypertension, red blood cell distribution width

Öz

Amaç: Bu çalışmanın amacı hipoksik iskemik ensefalopati(HİE) tanılı yenidoğanlarda tam kan sayımı parametrelerinin, pulmoner hipertansiyon (PH) ve kapak yetmezliği varlığının prognostik değerini incelemektir.

Gereç ve Yöntem: Sarnat ölçeğine göre evre 2 ve 3 HİE olan 115 term yenidoğan ile 90 sağlıklı yenidoğan hastanın verileri retrospektif olarak değerlendirilmiştir. İlk 6 saatteki ve hipotermi tedavisi sonrası 72.saatteki ekokardiyografik inceleme, kırmızı kan hücresi dağılım genişliği (RDW), trombosit dağılımı genişliği (PDW) ve CRP değerleri, kontrol grubu ile karşılaştırılmıştır.

Bulgular: Evre 3 HİE olan infantlarda tahmini ortalama sistolik ve diyastolik pulmoner arter basınçları evre 2 olan hastalara göre daha yüksek iken ejeksiyon fraksiyon değerleri evre 2 olanlara göre daha düşük bulunmuştur. İlk 6 saat ve 72. saatteki ortalama RDW, PDW ve CRP değerleri kontrol sağlıklı gruba göre hastalarda daha yüksek çıkmıştır. Özellikle evre 3 HİE hastalarında daha belirgin olmak üzere, bu parametrelerin 72.saatte ilk 6 saate göre önemli oranda arttığı görülmüştür.

Sonuç: Çalışmamız PH derecesi ve kapak yetmezliği varlığının, HİE'de prognozu belirlemede önemli parametreler olduğunu göstermektedir. RDW ve CRP gibi basit kan testleri ile ekokardiyografik değerlendirme yapılması yatış zamanı ve mortalite ile ilişkili olup prognozu belirlemede rehber olabilir.

Anahtar kelimeler: Ekokardiyografi, hipoksik-iskemik ensefalopati, pulmoner hipertansiyon, kırmızı kan hücresi dağılım genişliği.

Yazışma Adresi/Address for Correspondence: Gulcin Bozlu, Mersin University, Faculty of Medicine, Department of Pediatrics, Mersin, Turkey E-mail: gulnebi@hotmail.com
Geliş tarihi/Received: 11.11.2019 Kabul tarihi/Accepted: 05.12.2019 Published online: 17.12.2019

INTRODUCTION

Hypoxic-ischemic encephalopathy (HIE), which causes multiple organ dysfunction, is the most important cause of mortality and long-term morbidity in neonatal period [1,2]. The mortality rate has been reported as 10-60% in infants with HIE and developing myocardial dysfunction is one of the important determinants of prognosis[1,3,4]. The incidence of cardiac dysfunction ranges from 24 to 60% in perinatal asphyxia [5]. Although, various echocardiographic techniques have been used in evaluating reduced myocardial function in asphyxia, the parameters in prediction prognosis of the HIE have not been clearly demonstrated.

Neonates with HİE, cerebral ischemia initiates the congenital immune response in a short time and this brain damage is supposed to be responsible for the accumulation of inflammatory cytokines [6,7]. Red blood cell distribution width (RDW) and platelet distribution width (PDW) have already been known markers associated with severe inflammation [8,9]. High-sensitivity C-reactive protein (Hs-CRP), which is an acute phase protein, is also a sensitive indicator of inflammatory reactions [10,11]. Several studies have demonstrated the association of inflammatory cytokines with HIE [12,13]. Therapeutic hypothermia is the only accepted treatment modality in babies with HIE which gradually reduces the cellular metabolism. However, the role of these cytokines in the progression and prognosis of disease and the effect of hypothermia treatment is unclear.

Furthermore, there are no studies evaluating the relationship between RDW and/or PDW and prognosis of the disease in infants with HIE. The aim of this study is to investigate the prognostic value of pulmonary hypertension, cardiac valvular regurgitation and complete blood count parameters in neonates with HIE.

MATERIALS AND METHODS

In this retrospective study, 115 term newborns were screened in January 2012-December 2016 with the diagnosis of HIE who were hospitalized in neonatal intensive care unit. The diagnosis of HIE was based on American College of Obstetricians and Gynecologists criteria, and the severity of HIE was determined according to modified Sarnat staging [14,15]. The exclusion criteria were arriving to the center after six hours of birth, having gestational age less than 36 weeks, severe intrauterine growth retardation, the diagnosis of sepsis, congenital heart disease or other severe congenital anomalies. Patients who met the inclusion criteria and who were diagnosed with hypoxic-ischemic encephalopathy had ≤5 Apgar score at 10 minute, those who received positive pressure ventilation until 10 minute after delivery or with pH <7.0 or base excess ≤ -16 on blood gases analysis within the first hour after birth were evaluated. Amplitude integrated electroencephalography (aEEG) records (Brainz; Natus Medical, San Carlos, CA, USA) were kept for at least 30 minute if there were any finding(s) indicative of moderate or severe encephalopathy (i.e. lethargy, stupor, and coma), hypotonia, abnormal reflexes (i.e. pupil response to light), or convulsion. Patients were divided into two groups as moderate and severe.

Infants were cooled using the cool cap (OlympicMedical Cool Care System; OlympicMedical, Seattle, WA, USA) or tecotherm neo (Am Krümmling, Kabelsketal OT Zwintschöna, Germany) for 72 hours which was followed by rewarming over six hours. The aim was to maintain rectal temperature at 33–34°C for 72 hours. After cooling, the rectal temperature increased to 36.5°C (≤0.5°C/h). Serum samples were taken in the first six hours after birth and at 72 hours after rewarming.

Complete blood count (white blood cell count, platelet count, RDW, mean platelet volume, PDW) and CRP levels of all the patients and the control group were recorded. The control group consisted of 90 newborns admitted with the diagnosis of transient tachypnea of neonate with normal transthoracic echocardiography and similar in age and gender. Consents of the local ethics committee obtained (Mersin University Clinical Research Ethics Committee, 2017/178).

Echocardiography

Transthoracic echocardiography (TTE) by using 6 MHz transducers was performed to assess myocardial involvement in the first 24 hours after birth (Vivid S5 Pro Ultrasound System; GE Medical Systems, Horten, Norvay). Echocardiographic examinations were performed by the same experienced echocardiographer. The left ventricle

ejection fraction (LVEF) was calculated by using Simpson's biplane method. Cardiac valves were evaluated with evaluation annular and chordal pathologies, regurgitation and prolapses. Mitral and aortic valve regurgitations were assessed by colored Doppler echocardiography in apical and parasternal long axis windows. Tricuspit regurgitation jet and ventricular septal flattening were used to assess PH in conventional echocardiography. Systolic pulmonary arterial pressure (sPAPecho) was considered equal to the right ventricular (RV) systolic pressure in the absence of RV outflow tract (RVOT) obstruction or pulmonary stenosis (PS). The sPAPecho determined from the peak tricuspid regurgitation velocity as recommended using the modified Bernoulli equation considering the right atrial (RA) pressure gradient. The presence of persistent PH was recorded.

Statistical Analysis

The data processed and analyzed using the STATA MP/11 statistical package. Normality assumption of hemogram, echocardiographical values and hospitalization were checked by Shapiro Wilk test. These variables were summarized as mean and standard deviation and the comparisons between groups were performed using independent t-test or Mann-Whitney U test. The relationships between categorical variables were tested using Fisher's Exact test. The correlations between hospitalization and hemogram parameters were analyzed using Spearman correlation coefficient. The changes between the first and third days in groups were analyzed using t-test. Statistically significance level was accepted as less than 0.05.

RESULTS

During the period of study 185 newborns were diagnosed as HIE. Forty-two were excluded for not fulfilling the inclusion criteria. Fifteen were excluded because they aged more than six hours at the time of randomization, five was due to congenital malformation and eight were excluded because they were hemodynamically unstable and required recurrent resuscitation who then died. Therefore, study group included 115 patients and the control group included 90 patients. In the study group, 61 (53%) infants were staged as moderate and 54 (47%) infants as severe HIE (Figure 1).

Figure 1: Flow chart of patient selection

There were not any differences in mean gestational age, gender, birth weight, head circumference and type of delivery between the patient and control groups. Similarly, there was no difference in mean gestational age, birth weight and height, head circumference, and type of delivery in between moderate and severe HIE in study group ($p>0.005$) (Table 1).

Apgar score was significantly lower in Sarnat 3 patients than in Sarnat 2 patients as expected. The mean arterial blood gases pH in the first hour were 7.09 ± 0.11 and averaged base deficit 14.76 ± 3.62 in Sarnat 2 patients and pH 6.90 ± 0.16 and averaged base deficit was 19.04 ± 4.56 in Sarnat 3 patients. There were no significant differences in presence of hypotension, bradycardia, abnormal coagulation test, abnormal renal function tests, electrolyte imbalance, and elevation of liver enzymes between the patients in Sarnat 2 and Sarnat 3.

The estimated mean systolic and diastolic pulmonary artery pressure values were higher and ejection fraction was lower in the severe HIE group when compared with moderate HIE group ($p<0.001$, $p=0.001$). In the severe HIE group, hospitalization period was significantly longer ($p<0.001$) (Table 1). Correlation analysis revealed that systolic PAP ($p=0.001$, $r=0.426$) and diastolic PAP ($p=0.024$, $r=0.335$) showed a positive correlation with the duration of hospitalization. Fifteen of the patients in the study group died and 13 of them were in the Sarnat 3 group. There was a significant correlation between the presence of mitral regurgitation (MR), aortic regurgitation (AR), pulmonary hypertension, and death ($p<0.001$) (Table 2).

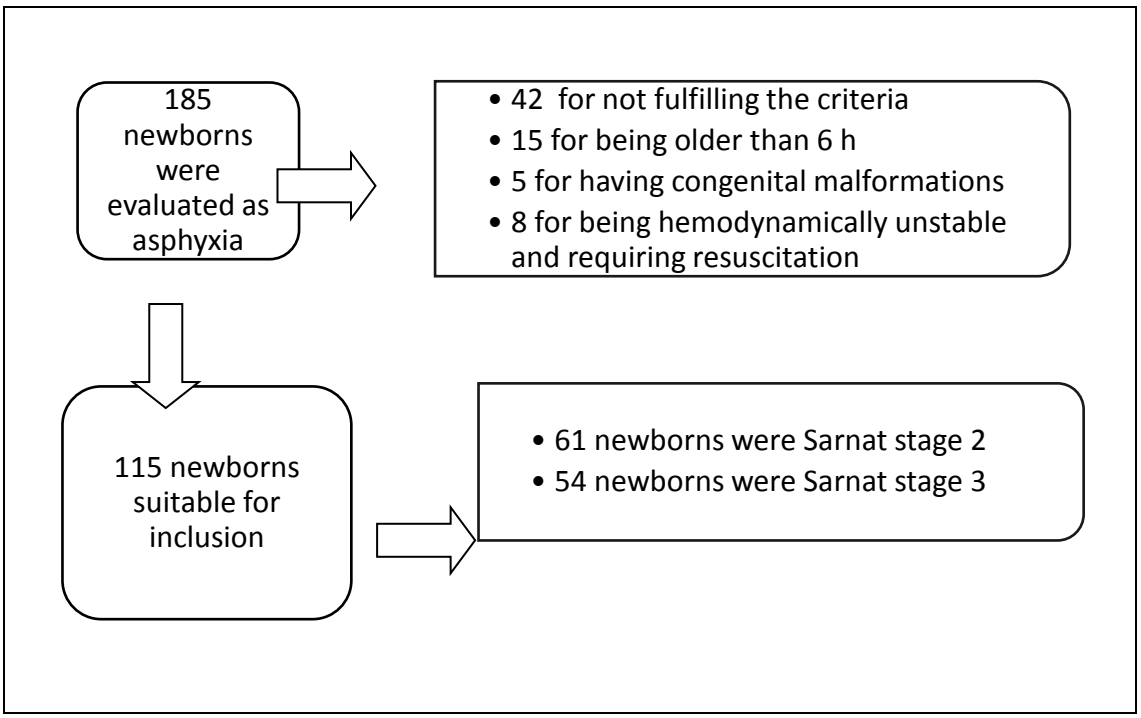

Table 1. Demographic and echocardiographic parameters of patients with Sarnat 2 and Sarnat 3

	Sarnat 2 (n=61)	Sarnat 3 (n=54)	p
Gestational age (week)	38.69±1.28	38.48±1.5	0.427
Birth weight (g)	3086.11±362	3041.77±639	0.748
Head circumference (cm)	34.85±0.67	34.88±1.99	0.933
Delivery Vaginal C-section	 37(60.7%) 24(39.3%)	 32(59.3%) 22(40.7%)	 0.142
Gender Male Female	 46(75.4%) 15(24.6%)	 29(53.7%) 25(46.2%)	 0.903
APGAR Score	5.0±1.0	4.1±1.4	<0.007
Hospitalization (day)	12.0±8.0	24.4±18.6	<0.001
sPAB (mmHg)	27.0±12.1	45.2±12.8	<0.001
dPAB (mmHg)	8.68±6.23	18.82±5.56	<0.001
EF	72.9±7.8	69.9±8.3	=0.001

sPAB: mean systolic pulmonary artery pressure, dPAB: mean diastolic pulmonary artery pressure, EF: ejection fraction.

Table 2. The correlation of mitral regurgitation, aortic regurgitation and presence of pulmonary hypertension with death in patients.

Parameter	Yes	No	p
Mitral regurgitation Death (Yes/No)	32 14/18	83 1/82	 <0.001
Aortic regurgitation Death (Yes/No)	15 10/5	100 5/95	 <0.001
Pulmonary hypertension Death (Yes/No)	17 15/2	98 98/0	 <0.001

Mean levels of RDW, PDW and CRP in the first six and 72 hours after birth were significantly higher in infants with HIE when compared with the control group ($p<0.05$) (Table 3). In the infants with HIE, there was a significant increase in these three parameters at 72 hours compared to the first six hours and this increase was more significant in the severe HIE group ($p<0.001$). The correlation between the increase in RDW and CRP values and the presence of AR, MR, pulmonary hypertension and death were significant ($p <0.05$ for all parameters).

Table 3. Mean RDW, PDW and CRP levels in the first 6 and 72 hours in patient and control groups

	Patient day 1	Patient day 3	Control day 1	Control day 3	p
RDW	17.76±2.42	18.16±2.63	17.01±1.68	15.85±2.5	<0.001
PDW	13.29±3.71	16.3±3.22	14.6±2.88	14.55±2.43	<0.001
CRP	3.4±6.96	20.15±31.86	1.28±2.31	1.41±1.13	<0.001

RDW: red cell distribution width, PDW: platelet distribution width

DISCUSSION

This is the first study to evaluate the association of RDW, PDW and CRP with cardiac involvement and prognosis in infants with HIE treated with therapeutic hypothermia and rewarming therapy. In this study, it was determined that the degree of pulmonary hypertension and valvular regurgitation were important parameters in determining the prognosis in HIE. Moreover, mean values of RDW and CRP, which were significantly higher in HIE infants, were increased after 72 hours and this increase was demonstrated to be correlated with presence of MR, AR, persistant pulmonary hypertension and death.

The severity and duration of perinatal asphyxia determines the development of post-asphyxia cardiac dysfunction. In our study, the predicted mean systolic and diastolic pulmonary artery pressures were higher and the ejection fraction was significantly lower in patients with severe HIE than moderate HIE. In some studies, using several echocardiographic measurements have shown that ventricular functions decrease in asphyxiated infants with respect to controls [4,16,17]. In asphyxiated infants, especially in the first two days, left ventricular dysfunction may occur that may lead to end-organ hypoperfusion and further increase the hypoxic / acidotic state [4,17].

Another important problem in asphyxiated infants is pulmonary hypertension which is caused by hypoxia. Especially, refractory persistent pulmonary hypertension or persisting fetal circulation is an important clinical condition that increases infant morbidity and mortality. In asphyxiated infants, the pulmonary artery pressure has been reported to be higher in the first seven days after birth than in healthy subjects. The resulting pulmonary hypertension is thought to be associated with ventricular dysfunction [18]. Persistent pulmonary hypertension in asphyxiated infants is possibly caused by direct effects of hypoxia and acidosis on pulmonary vascular resistance or may be related with meconium aspiration syndrome and associated with morbidities [19]. In a study including 40 term infants with HIE on the first day of life, the rate of pulmonary arterial diastolic pressure, pulmonary arterial resistance, and pulmonary arterial resistance to systemic resistance ratio were significantly higher in patients than healthy newborns [20]. Aggarwal et al.[18], reported that eccentricity indices and right ventricular systolic to diastolic duration ratio, which are the pulmonary hypertension parameters, in infants with HIE were significantly deranged. In this study, they found out that the duration of hospitalization in severe HIE group was significantly longer which had a positive correlation with systolic and diastolic PAP. In addition, there was a significant relationship between the presence of valvular regurgitation (MR, AR) and persistent pulmonary hypertension and death. In the literature, it has been reported that the echocardiography parameters were usually not used in determining the risk of death in patients with HIE. It was reported that no significant predictive value could be shown for mortality with shortening fraction and tissue Doppler imaging in the evaluation of 25 asphyxiated newborn in the first 72 hours [16]. In another study in 34 term newborns with mild and severe HIE, nine

patients died and only one of them had a slight reduction in the ejection fraction in the first 24-48 hours of life [21]. On the contrary, Aggarwal et al. showed that there was a significant difference of the mean eccentricity indices between survived and died patients [18]. In our study, 15 of the patients died and 13 of them were in the severe HIE group. Presence of a significant association between valvular regurgitation and persistent pulmonary hypertension suggests that echocardiography can be used to predict severe pulmonary hypertension and consequently prognosis in patients with severe HIE especially.

Ischemia in the brain causes the inflammatory response of both the brain parenchyma and systemic circulation. In the newborn, cerebral ischemia results an immune response triggered within a few minutes [6]. There are strong evidences that oxidative stress plays an important role in HIE pathogenesis and progression [22]. Oxidative stress and consecutive post-ischemic inflammation are responsible for exacerbation of brain damage [6,22]. Oxidative stress and chronic inflammation cause shortening of erythrocyte life span and increase in numbers of different sized and immobile erythrocytes in circulation [8]. It has been emphasized that RDW that reflects the variability in the size of red blood cells in circulation, increases in some heart diseases and is assumed to be a strong risk factor for predicting mortality [23,24]. PDW level that shows variability in platelet size and it can be used as platelet activation markers. Studies have reported that PDW reflects the severity of inflammation and detected at higher levels in myocardial infarction and chronic pulmonary diseases [9]. Thus, it has been shown that high RDW and PDW levels are associated with the pro-inflammatory situations [8,9]. Similarly, CRP is one of the well-known inflammatory markers [25,26]. In our study, increased levels of RDW, PDW and CRP in patients suggest that these parameters are both markers of inflammation and increase the risk of cardiovascular diseases. Moreover, these parameters increased at the end of 72 hours of life in infants with HIE significantly compared to the first six hours and the increase was more significant in severe HIE group. This supports the hypothesis that oxidative stress and inflammation are more serious in severe hypoxic group.

One of the most important problems determining the prognosis in patients with HIE is the degree of pulmonary hypertension. The relationship between pulmonary hypertension and RDW has been investigated. It is suggested that elevated RDW level is superior to the other potential biomarkers in circulation in pulmonary hypertension. Recently, it has been demonstrated that high levels of inflammatory molecules can predict survival in patients with pulmonary hypertension independent from the hemodynamic measurements [27]. Wang W et al.[28], found that RDW levels in patients with chronic thromboembolic pulmonary hypertension were higher than controls. Besides, they suggested that RDW is an independent marker in the diagnosis of this disease. However, RDW has never been studied in HIE. In our study, increased RDW and CRP values in repeated measurements during the first day in HIE group, associated with the presence of pulmonary hypertension and death, suggest that RDW and CRP could be used in follow up and prognosis of infants with severe HIE. The study also suggests that increased RDW and CRP values at follow up were significantly associated with MR and AR. These results also support the role of oxidative stress and chronic inflammation in physiopathology of HIE, and also support the association of RDW and CRP with inflammation.

In conclusion, in this study, mean values of RDW and CRP have been shown to be related with valvular regurgitation, presence of pulmonary hypertension and death. Increased RDW and CRP values especially in infants with severe HIE, which is associated with the severity of pulmonary hypertension and death, suggests that these parameters may be used as risk indicators for prognosis in infants with HIE. A strong inflammatory response triggered by HIE resulting in post-ischemic inflammation is associated with the exacerbation of brain injury. In addition, increased risk of persistent PH in asphyxiated infants has the potential to affect the prognosis of disease. Therefore, we believe that functional echocardiography can be used in the diagnosis and follow up of infants with persistent PH and those markers such as RDW and CRP, which are easy to access and which reflect the inflammatory process, may be helpful in monitoring therapeutic efficacy. However, a wide range of prospective studies are required in order to clarify this complex relationship.

The most important limitation of this study was being retrospectively designed. Besides

inflammation, parameters such as erythropoietin, iron, folic acid, and fibrinogen, which are known to affect RDW levels, have not been studied. However, both the patient and study group did not include newborns with anemia or any hematologic problems.

Yazar Katkıları: Çalışma konsepti/Tasarımı: DK,YÇ, DD, FD Veri toplama: DK,YÇ,DD,FD,GB,DG,BK,OHK; Veri analizi ve yorumlama: DK,YÇ,DD,FD,GB,DG,BK,OHK; Yazı taslağı: DK,YÇ,DD,FD,GB,DG,BK,OHK; İçeriğin eleştirel incelenmesi: DK,YÇ,DD,FD,GB,DG,BK,OHK; Son onay ve sorumluluk: DK,YÇ,DD,FD,GB,DG,BK,OHK; Teknik ve malzeme desteği: DK,YÇ,DD,FD,GB,DG,BK,OHK;;Süpervizyon: DK,YÇ,DD,FD,GB,DG,BK,OHK; Fon sağlama (mevcut ise): yok.
Hakem Değerlendirmesi: Dış bağımsız.
Çıkar Çatışması: Yazarlar çıkar çatışması beyan etmemişlerdir.
Finansal Destek: Yazarlar finansal destek beyan etmemişlerdir.
Author Contributions: Concept/Design : DK,YÇ, DD, FD ; Data acquisition: DK,YÇ,DD,FD,GB,DG,BK,OHK; Data analysis and interpretation: DK,YÇ,DD,FD,GB,DG,BK,OHK; Drafting manuscript: DK,YÇ,DD,FD,GB,DG,BK,OHK; Critical revision of manuscript: DK,YÇ,DD,FD,GB,DG,BK,OHK; Final approval and accountability: DK,YÇ,DD,FD,GB,DG,BK,OHK; Technical or material support: DK,YÇ,DD,FD,GB,DG,BK,OHK; Supervision: DK,YÇ,DD,FD,GB,DG,BK,OHK; Securing funding (if available): n/a.
Peer-review: Externally peer-reviewed.
Conflict of Interest: Authors declared no conflict of interest.
Financial Disclosure: Authors declared no financial support

REFERENCES

1. Jacobs SE, Berg M, Hunt R, Tarnow-Mordi WO, Inder TE, Davis PG. Cooling for newborns with hypoxic ischaemic encephalopathy. Cochrane Database Syst Rev. 2013;(1):CD003311.
2. Takenouchi T, Iwata O, Nabetani M, Tamura M. Therapeutic hypothermia for neonatal encephalopathy. Brain Dev 2012;34:165-70.
3. Shah P, Riphagen S, Beyene J, Perlman M. Multiorgan dysfunction in infants with post-asphyxial hypoxic-ischaemic encephalopathy. Arch Dis Child Fetal Neonatal Ed. 2004;89:152-55.
4. Nestaas E, Skranes JH, Støylen A, Brunvand L, Fugelseth D. The myocardial function during and after whole-body therapeutic hypothermia for hypoxic–ischemic encephalopathy, a cohort study. Early Hum Dev. 2014;90:247-52.
5. Adcock LM, Papile LA. Perinatal asphyxia. In Manual of neonatal care. 6th edition. Edited by Cloherty JP, Eichenwald EC, Stark AR. New Delhi: Wolters Kluwer. 2008:518-23.
6. Liu F, McCullough LD. Inflammatory responses in hypoxic ischemic encephalopathy. Acta Pharmacol Sin. 2013;34:1121-30.
7. Bonestroo HJ, Nijboer CH, van Velthoven CT, Kavelaars A, Hack CE, van Bel F at al. Cerebral and hepatic inflammatory response after neonatal hypoxia-ischemia in newborn rats. Dev Neurosci. 2013;35:197-211.
8. Zalawadiya S.K, Veeranna V, Niraj A, Pradhan J, Afonso L. Red cell distribution width and risk of coronary heart disease events, Am J Cardiol 2010; 106:988-93.
9. Endler G, Klimesch A, Sunder-Plassmann H, Schillinger M, Exner M, Mannhalter C et al. Mean platelet volume is an independent risk factor for myocardial infarction but not for coronary artery disease. Br J Haematol. 2002;117:399-404.
10. Yousuf O, Mohanty BD, Martin SS, Joshi PH, Blaha MJ, Nasir K et al. High-sensitivity C-reactive protein and cardiovascular disease: a resolute belief or an elusive link? J Am Coll Cardiol. 2013;62:397-408.
11. Shang Y, Mu L, Guo X, Li Y, Wang L, Yang W et al.Clinical significance of interleukin-6, tumor necrosis factor-αand high-sensitivity C-reactiveprotein in neonates with hypoxic ischemic encephalopathy. Exp Ther Med. 2014;8:1259-62.
12. Aly H, Khashaba MT, El-Ayouty M, El-Sayed O and Hasanein BM. IL-1beta, IL-6 and TNF-alpha and outcomes of neonatal hypoxic ischemic encephalopathy. Brain Dev. 2006;28:178-82.
13. Windgassen EB, Funtowicz L, Lunsford TN, Harris LA and Mulvagh SL. C-reactive protein and high-sensitivity C-reactive protein: an update for clinicians. Postgrad Med. 2011;123:114-19.
14. American College of Obstetricians and Gynecologists (ACOG). Neonatal encephalopathy and cerebral palsy: Executive summary. Obstet Gynecol. 2004;103:780-81.
15. Levene MI, de Vries L. Hypoxic-ischemic encephalopathy. In: Martin RJ, Fanaroff AA, Walsh MC (eds). Neonatal-Perinatal Medicine, 8th edn. Elsevier, Philadelphia. 2006;938-56.
16. Matter M, Abdel-Hady H, Attia G, Hafez M, Seliem W, AlArman M. Myocardial performance in asphyxiated full-term infants assessed by Doppler tissue imaging. Pediatr Cardiol. 2010;31:634-42.
17. Van Bel F, Walther FJ. Myocardial dysfunction and cerebral blood flow velocity following birth asphyxia. Acta Pediatr Scand. 1990;79:756-62.
18. Aggarwal S, Natarajan G. Biventricular function on early echocardiograms in neonatal hypoxic–ischaemic encephalopathy. Acta Paediatr. 2017;106:1085-90.
19. Lapointe A, Barrington KJ. Pulmonary hypertension and the asphyxiated newborn. J Pediatr. 2011;158:19-24.
20. Liu J, Feng ZC. Changes in pulmonary arterial pressure in term-infants with hypoxic–ischemic encephalopathy. Pediatr Int. 2009;51:786-89.
21. Kanik E, Ozer EA, Bakiler AR, Aydinlioglu H, Dorak C, Dogrusoz B et al. Assessment of myocardial dysfunction in neonates with hypoxic-ischemic encephalopathy: Is it a significant predictor of mortality? J Matern Fetal Neonatal Med. 2009;22:239-42.

22. Zhao M, Zhu P, Fujino M, Zhuang J, Guo H, Sheikh I et al. Oxidative Stress in Hypoxic-Ischemic Encephalopathy: Molecular Mechanisms and Therapeutic Strategies. Int J Mol Sci. 2016;10:17-29.
23. Emans ME, Gaillard CA, Pfister R, Tanck MW, Boekholdt SM, Wareham NJ et al. Red cell distribution width is associated with physical inactivity and heart failure, independent of established risk factors, inflammation or iron metabolism; the EPIC-Norfolk study. Int J Cardiol. 2013;168:3550-55.
24. Isik T, Uyarel H, Tanboga IH, Kurt M, Ekinci M, Kaya A et al. Relation of red cell distribution width with the presence, severity, and complexity of coronary artery disease. Coron Artery Dis. 2012;23:51-6.
25. Hofer N, Zacharias E, Muller W, Resch B. An update on the use of C-reactive protein in early-onset neonatal sepsis: current insights and new tasks. Neonatology. 2012;102:25-36.
26. Chakkarapani E, Davis J, Thoresen M. Therapeutic hypothermia delays the C-reactive protein response and suppresses white blood cell and platelet count in infants with neonatal encephalopathy. Arch Dis Child Fetal Neonatal Ed. 2014;99:458-63.
27. Hampole CV, Mehrotra AK, Thenappan T, Gomberg-Maitland M, Shah SJ. Usefulness of red cell distribution width as a prognostic marker in pulmonary hypertension. Am J Cardiol. 2009;104:868-72.
28. Wang W, Liu J, Yang Y, Zhai Z, Wang C, Wang J. Red cell distribution width is increased in chronic thromboembolic pulmonary hypertension. Clin Respir J. 2016;10:54-60.