RESEARCH ARTICLE

OPEN ACCESS

CRANIAL ULTRASOUND: EFFICIENT SCREENING TOOL FOR EARLY DETECTION OF BRAIN INJURY IN PRETERM INFANTS

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Received: October 5, 2019

Accepted: September 29, 2020

Published: January 1, 2020

Cite this as:

Erawati DR, Yueniwati Y.
Cranial ultrasound: efficient
screening tool for early detection
of brain injury in preterm infants.
Malang Neurology Journal;
2021.7:7-11.
<http://dx.doi.org/10.21776/ub.mnj.2021.007.01.2>

ABSTRACT

Background: Cranial ultrasound becomes an important diagnostic tool to evaluate brain injury in infants. Brain injury is a major complication for preterm birth. The brain injury of preterm infants differs from that of a term infant. Brain injury has correlation with gestational age and mode of delivery.

Objective: To analyze the correlation between cranial ultrasound findings with gestational age and mode of delivery and to reveal if cranial ultrasound can be used to detect brain injury in premature infants.

Methods: An observational analytic study using cross-sectional design took place in Saiful Anwar Hospital Malang, Indonesia. 38 healthy preterm infants underwent cranial ultrasound examination within the first four day of life. Fisher Exact test was used to analyze the correlation between cranial ultrasound findings with gestational age and mode of delivery.

Results: Most of the healthy preterm infants (89.5%) were 32 weeks gestational age, and 52.6% of samples had caesarean section as their mode of delivery. There were three abnormal findings in cranial ultrasound; increased periventricular echogenic (5.3%), increased parenchym echogenic (5.3%), and indistinguishable of gray-white matter differentiation (5.3%). There was no significant correlation between abnormal cranial ultrasound findings with gestational age and mode of delivery ($p=0.202$; $p=0.218$).

Conclusion: There were abnormal cranial ultrasound findings in some healthy preterm infants despite no significant correlation between ultrasound findings with gestational age and mode of delivery. Cranial ultrasound in preterm infants could become a screening tool for early detection of brain injury.

Keywords: Brain injury, cranial ultrasound, healthy preterm infants, gestational age, mode of delivery

Introduction

Preterm births remain as a major challenge in prenatal health. The World Health Organization (WHO) in 2018 stipulated that every year, an estimated 15 million babies are born preterm (before completing the 37 weeks of gestation), and this number is rising.^{1,2}

Preterm birth complications are the leading cause of death among children under 5 years of age, responsible for approximately 1 million deaths in 2015. Preterm births are the major cause of neonatal mortality and nearly half of all cases have had congenital neurological disorders including cerebral palsy. Although all births less than 37 weeks are classified as preterm births, the births less than 32 weeks' gestation comprise the highest mortality and neonatal disorders.^{3,4}

Brain injury is a major complication of preterm birth. It puts the infants that survive in conditions at risk of developmental disorders, cognitive dysfunction, and impaired manner. The brain injury of preterm infants differs from that of full-term infant. The most significant development differences that occur in the third semester

pregnancy is the maturation of pressure-passive circulation, involution of the germinal matrix, selective stage-dependent differences in vascular white matter, and the sensitivity of oligodendrocyte against hypoxic injury. Cerebral injuries, such as white matter lesion and intra ventricular hemorrhage, are considered the cause of neurological disorders in preterm infants.^{5,6}

A large number of prenatal risk factors with different capacities in terms of prediction of neurologic developmental disorders have been identified. Some multiple risk factors increase the risk of disability, which may act as additional effector multiplication effect. Some examples of prenatal risk factors are antepartum hemorrhage, congenital infections, preeclampsia, mode of delivery, short gestational age, microcephaly, and congenital anomalies. In addition, socio-economic status, parental education, maternal age, and parity also influence the outcome of the abnormality.^{4,7,8}

Cranial ultrasound has become an important diagnostic tool since the 1970's. Its non-invasive nature has caused the ultrasound to become an ideal imaging modality in neonates. The fontanel and other structures of neonates and

young infants are still open, thus allowing them to be the acoustic window for evaluating the brain. The cranial ultrasound examination has several advantages, among which are: minimal manipulation in infants, safe, repeatable so that it can evaluate the evolution maturation and lesions in the brain, and reliable in detecting brain pathology (such as hemorrhage, cystic lesions, ischemia, calcified, infection of the brain, and brain structures of major anomalies). In addition, the cranial ultrasound is relatively cheap compared to other neurological imaging modalities and is also a good modality for serial brain imaging for the neonates.^{8,9}

Preterm infants who are clinically healthy have the possibilities of having brain injury that could not be visualized on ultrasound examination. It means, the visible abnormalities on ultrasound sometimes do not provide significant clinical symptoms or are asymptomatic. Some research literature mentioned that in spite of full term or near-full term gestation and declared as healthy, infants could show an abnormality by cranial ultrasound imaging.^{10,11} Research by Mercuri et al in 1998 on healthy infants born with a gestational age between 36 and 42 weeks showed abnormalities in the cranial ultrasound examination in 35 out of 177 infants; mostly ischemic (periventricular and thalamus) and hemorrhagic lesions.¹²⁻¹⁴ Research by Hagmann et al in 2010 on healthy infants born full term in Uganda showed abnormalities presented by the cranial ultrasound examination in 55 from 112 infants; in the form of an increase in white matter echogenic, subependymal cysts, and choroid plexus cysts.¹³

Wang et al in 2004 found 6 from 2309 (0.26%) full term healthy infants have major brain lesions, such as intra ventricular hemorrhage, intra parenchymal bleeding and corpus callosum agenesis.¹⁵

In order to prevent the missing prognostic abnormalities, a screening protocol in the form of cranial ultrasound examination should be conducted at least four or five times. The first examination should be conducted as early as possible in order to detect long-term intra-uterine damage or congenital malformations. It is important to be sure whether the results appear normal at this time, whether the anatomy looks normal for the infant's gestational age, whether there is not a picture of a congenital infection or metabolic disease, and to generate baseline data for management problems that could arise later, such as bleeding or echogenic of white matter.^{8,9}

This study aimed to find the relationship between the cranial ultrasound findings with the gestational age and mode of delivery and to reveal if the cranial ultrasound can be used to detect brain injury in healthy preterm infants in Saiful Anwar Hospital Malang, Indonesia.

Methods

This study was an observational-analytic with a cross-sectional design, conducted in the perinatology and ultrasound room of the Saiful Anwar Hospital Malang. The protocol has been approved by the Medical Research Ethics Committee of the Medical Faculty of Universitas Brawijaya Malang No: 352/KEPK/VII/2012. A total of 38 healthy preterm infants were included in this study. The inclusion criteria of the study subjects were healthy preterm infants at

the age of 4 days. Infants who have congenital abnormalities were excluded from the study.

Medical records and anamnesis were used to collect data on gestational age and mode of delivery. The cranial ultrasound was performed by three radiologists who have experiences in their field for at least 10 years. In order for the diagnosis to be positive, a minimum of two examiners statements is needed. The examination was performed using an ultrasound (General Electric Logic S6 series, USA) with a curved transducer (5MHz) and linear transducer (10MHz) and was conducted with the anterior fontanel window and six coronal pieces and five sagittal pieces. Relationships between the gestational age and mode of delivery with a cranial ultrasound imaging were tested using the Fisher Exact test with a 95% confidence level, = 0.05 significant when $p < 0.05$.

Results

Out of the 38 preterm infants, 52.6% of them were female and 47.4% were male. A total of 52.6% of the infants were born through caesarian section. Most of the infants were 32 weeks (89.5%) and had birth weight between 1500 and 2500 grams.

Cranial ultrasound examination showed three kinds of abnormal imaging, which were the increased periventricular echogenic, increased parenchymal echogenic, and indistinguishable gray-white matter differentiation (Table 1).

Table 1. Cranial ultrasound results

	n (%)
Periventricular echogenic	
Increased	2 (5,3)
Not increased	36 (94,7)
Parenchymal echogenic	
Increased	2 (5,3)
Not increased	36 (94,7)
White-gray matter differentiation	
Indistinguishable	2 (5,3)
Distinguishable	36 (94,7)

Two infants revealed increased periventricular echogenic (5.3%); one infant with an increase in the right lateral superior periventricular and the other one in the caudo-thalamic notch (Figure 1).

Two infants were found to have increased parenchymal echogenic (unilateral and focal thalamus echogenic) (5.3%) (Figure 2).

The indistinguishable differentiation of gray-white matter was discovered in two infants (5.3%). Distinguishing between the cortical and sub-cortical was difficult to perform in both infants (Figure. 3).

It was found that in 34 infants with a gestational age 32 weeks, 3% of them had an increase in periventricular echogenic, while in infants with gestational age < 32 weeks, 25% of them had it. Increased parenchymal echogenic was found in 6% of infants with gestational age 32 weeks. The indistinguishable gray-white matters were found as much as 3% in the gestational age group 32 weeks and 25% in the gestational age group < 32 weeks. There were differences in the proportion of each variable of cranial ultrasound based on the gestational age, but the differences were not statistically significant ($p > 0.05$)

Table 2. The results of cranial ultrasound based on the gestational age

Gestational age	Periventricular echogenic			Parenchymal echogenic			Gray-white matter differentiation		
	Increased (%)	Not Increased (%)	p	Increased (%)	Not Increased (%)	p	Indistinguishable (%)	Distinguishable (%)	p
< 32 weeks	1 (25)	3 (75)	0,202	0 (0)	4 (100)	0,798	1 (25)	3 (75)	0,202
≥ 32 weeks	1 (3)	33 (9)		2 (6)	32 (94)		1 (3)	33 (97)	

Significant $p < 0.05$ **Table 3.** The results of cranial ultrasound based on the mode of delivery

Mode of delivery	Periventricular echogenic			Parenchymal echogenic			Gray-white matter differentiation		
	Increased (%)	Not Increased (%)	p	Increased (%)	Not Increased (%)	p	Indistinguishable (%)	Distinguishable (%)	p
Spontaneous	2 (11)	16 (89)	0,218	0 (0)	18 (100)	0,270	2 (11)	16 (89)	0,218
Section caesarean	0 (0)	20 (100)		2 (10)	18 (90)		0 (0)	20 (100)	

Significant $p < 0.05$ **Table 4.** The results of cranial ultrasound based on the combination of mode of delivery and gestational age

	Periventricular echogenic			Parenchymal echogenic			Gray white matter differentiation		
	Increased (%)	Not Increased (%)	p	Increased (%)	Not Increased (%)	p	Indistinguishable (%)	Distinguishable (%)	p
Spontaneous and ≥ 32 weeks	1 (7,1)	13 (92,9)	0,114	0 (0)	14 (100)	0,387	1 (7,1)	13 (92,9)	0,114
Spontaneous and < 32 weeks	1 (25)	3 (75)		0 (0)	4 (100)		1 (25)	3 (75)	
Section caesarean and ≥ 32 weeks	0 (0)	20 (100)		2 (10)	18 (90)		0 (0)	20 (100)	

Significant $p < 0.05$

It was found that in 18 infants with spontaneous birth, 11% of them had increased periventricular echogenic. On the other hand, there was no such image found from the 20 infants with caesarean section birth. No increase in parenchymal echogenic was present on the infant group with spontaneous birth. The white gray matter differentiation was found in 10% infants with spontaneous birth. However, it was not discovered in the group of infants with caesarean section birth. There were differences in the proportion of each variable of cranial ultrasound based on the mode of delivery, but the differences were not statistically significant ($p > 0.05$).

Statistical analysis showed that there is no significant correlation between the results of cranial ultrasound with the combination of gestational age and mode of delivery ($p > 0.05$).

Discussion

The samples obtained in this study were 38 preterm infants, 18 of whom were male and 20 were female. There were 34 infants with gestational age ≥ 32 weeks and 4 infants with gestational age < 32 weeks. Macones stated that birth at less than 32 gestational weeks has the highest mortality and neonatal disorders. After 32 gestational weeks, there was a noticeable increase in vascular system and the number of anastomosis in the deep white matter, and thus changing the pattern of injury.^{3,16}

A total of 18 infants were delivered spontaneously, and 20 infants were born through caesarean section. Previous study showed that birth by emergency cesarean, with or without a prior attempt of vaginal births, correlated with high intracranial hemorrhage compared to spontaneous birth, whereas the incidence of brain hemorrhage in elective cesarean did not differ significantly with the spontaneous births.

This research found two infants with an increased periventricular echogenic: one infant with ≥ 32 gestational weeks with a lesion in the lateral superior ventricles, and another infant with a gestational age < 32 weeks with a lesion in the caudo-thalamic notch with ventricular asymmetry. Both underwent spontaneous delivery. It is likely for a preterm infant with a hyper-echoic lesion in the periventricular to have a white matter injury, but edema can also present such image and show improvements without any further brain damage.^{3,17} Increased periventricular echogenic might show a normal condition if it lasts less than a week. Infants with increased echogenic in the caudo-thalamic notch require further observation because the lesions in this area are probably a germinal matrix hemorrhage which usually occurs in preterm infants.¹⁸

Figure 1. USG examination result with increased echogenic A) Right Anterior Periventricular (yellow arrow) is more increased than the left side, B) periventricular (caudothalamic notch)

Figure 2. USG examination result with increased unilateral echogenic and focal in left thalamus (yellow arrow)

Figure 3. Indistinguishable differentiation of gray-white matter (yellow arrow)

Two infants had unilateral increased echogenic in the thalamus. The density of unilateral thalamus in preterm infants was reported by de Vries (1992) and van Wezel-Meijlrin (1999) and it is related to severe asphyxia condition and treatment of longer ventilation, although the prognosis is better than infants who have bilateral lesions of the thalamus.¹³ However, the studies on healthy full-term infants in Uganda found that unilateral lesions of the thalamus also occur in asymptomatic infants. This study found two infants had increased unilateral and focal thalamus echogenic, in which both the infants had a gestational age 32 weeks with caesarean section mode of delivery. Both may not be related to global hypoxic ischemic. Infarction in the territory of the perforator artery can explain these ultrasound findings, because the perforator artery is not always associated with acute

symptoms. Unilateral abnormalities can also be thalamus hemorrhage, which is associated with venous thrombosis, usually accompanied with intra ventricular hemorrhage and clinical seizures in the patient. This study did not find any intra ventricular hemorrhage image in the ultrasound findings.^{13,14}

The indistinguishable gray-white matter was found in one infant in each gestational age group 32 weeks and < 32 weeks. Both infants were delivered spontaneously. The visualized cortical structures became more hyper-echoic, making it difficult to distinguish from the subcortical structures. The edema conditions could give such image and will improve without any further brain damage. In this study, there was no increased intracranial pressure in all infants.^{7,19}

Statistically, there was no significant correlation between abnormal ultrasound findings (increased periventricular echogenic, increased parenchymal echogenic, and gray-white matter differentiation) with the gestational age and mode of delivery. A similar studies on full term infants with more samples also showed that there was no correlation between ultrasound findings with gestational age and mode of delivery. The research conducted by Behnke et al 1999 on 266 infants with cranial ultrasound examination within 96 hours of birth age found that there was no significant correlation between neurobehavior status with head ultrasound abnormalities findings. Therefore, it was concluded that ultrasound abnormalities found within 96 hours of life have no clinical significance in the neonatal period. The data in this study was obtained within 4 days, and therefore it is still possible that the cranial ultrasound findings are light findings and do not affect the clinical condition of the infants.^{5,14}

Conclusion

There are abnormal cranial ultrasound findings in some healthy preterm infants, although there is no significant correlation between ultrasound findings with gestational age and mode of delivery. Cranial ultrasound in preterm infants can become a screening tool for an early detection of brain injury.

Acknowledgement

This work was supported by grants from Faculty of Medicine, Universitas Brawijaya, Malang, Indonesia

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