Original Article

Serial Cranial Ultrasound Studies in Preterm Infants

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Objective: To study reasonable timing for repeating head ultrasound screenings (HUS) in preterm infants and to find out any change in severity of intraventricular hemorrhage.

Materials and Methods: Medical records and ultrasound findings of all preterm infants younger than 32 weeks gestational age (GA) admitted to the neonatal intensive care unit (NICU) at Phramongkutklao Hospital between January 1, 2014 and December 31, 2018 were reviewed retrospectively.

Results: One hundred thirty-three infants were included in the present study. Eighty-five infants had at least two HUS and included in discrimination analysis. The positive predictive value for having a normal HUS after two previously normal studies seven or more days apart was 89.30% with a specificity of 80%. Of the 24 preterm infants with IVH, 19 had repeated the cranial ultrasound. This revealed that repeating HUS early (day 7 or earlier), 90% (9/10 infants) found no change in finding, whereas repeating HUS at day 30 or later revealed as high as 76.4% change in findings.

Conclusion: Routine screening of cranial ultrasound examinations are recommended for all infants born before 32 weeks GA. If the scan is abnormal, repeating the scan at day 30 or later may be more helpful than as early as day 7. However, if the scan showed no abnormality and had been repeated seven or fewer days apart with the same negative result, subsequent scan may not add benefits. However, these findings need to be proved and may be used only as a guide to design a prospective study in the future.

Keywords: Preterm infant, Screening cranial ultrasound, Intraventricular hemorrhage

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Preterm infants are at risk to have several kinds of intracranial abnormalities. Intraventricular hemorrhage (IVH) is a serious complication that can be found in preterm infants, accounting about 25 percent. Such incidence, together with severity levels, is an inverse relation to gestational age (GA) and birth weight (BW)[1]. Some abnormalities affect the development of the brain in the long term, for example, a cerebral palsy. Consequently, it is necessary for every neonate to have a head ultrasound screening (HUS). However, if the ultrasound is screened too soon, it may result in false negative results and negatively affect the long-term development of their brains. On the other hand, screening too late may also lead to morbidity and mortality. Many guidelines have been proposed for the proper schedule of ultrasound screening in preterm infants. For example, the guideline for neonatal cranial ultrasound of the Southern Health and Social Care Trust[2] recommends to start screening in the infants who are younger than 33 weeks GA and to repeat the screening at day 3, day 7 to 10, day 28, and term-equivalent age for the infants that are younger than 30 weeks GA. For infants at 30 to 32 weeks GA, the repeating scan will be on day 7 to 10 and at term-equivalent age. To scan on the first day of life was under the clinician discretion in both age groups.

Another guideline from the neonatal intensive care unit (NICU) of John Hunter Children's Hospital[3] recommends for preterm infants whose GA is younger than 30 weeks or BW is less than 1,250 grams to receive the ultrasound screening with the first screening on day 5 to 7 and the second screening on day 28.

In the authors' hospital, there has been no study

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regarding either the proper timing to screen or the proper time to repeat the scan. In clinical practice, it was encouraged to start in preterm infants weighing less than 1,500 grams and usually be repeated at 1 to 2 days, 7 days, and 28 to 30 days of life. However, because the HUS is expensive, and the pediatric radiologists are insufficient, it is sometimes difficult to follow this recommendation. Therefore, the objectives of the present study were to study for the proper timing to repeat HUS in preterm infants and to monitor any changes in abnormality detected from the screening in an attempt to establish an appropriate guideline in the future.

Materials and Methods

Target population

The present study was a retrospective study conducted in preterm infants younger than 32 weeks GA admitted to the NICU at Phramongkutklao Hospital between January 1, 2014 and December 31, 2018. Included patients were the ones examined by the cranial ultrasound either at the Department of Radiology by an experienced pediatric radiologist (Khampunnip S), or, at the NICU by an experienced neonatal pediatrician (N.S., T.S., C.M.). An exclusion criterion was infants whose cranial ultrasounds were performed at other hospitals (referred cases).

Sample size estimation

Sample size was calculated based on the incidence of IVH in preterm infants obtained from the literature review of Inder et al[1], using an equation $n = [Z^2_{\alpha/2}P(1–P)]/d^2$, while n=sample size, p=the incidence of IVH in preterm infants (25%), d=error (0.05), and $Z_{\alpha/2}$=standard values from table Z at α=0.05 (1.96). Then, the number of infants included was 288.12 (289).

Evaluation process and data collection

The present study was approved by the Institutional Review Board Royal Thai Army Medical Department (ID: R124h/62_Exp). The Permission to access medical records and ICD-10 was given by the director of Phramongkutklao Hospital (ICD-10=P52.0, P91.2, P.90.82 and Q04.8). Medical records and the picture archiving and communication system (PACS) were reviewed and recorded. Demographic data and medical information collected included date of birth, BW, GA, delivery route, Apgar scores, hospital length of stay (LOS), dates and reports of HUS studies, and the occurrences of medical complications for those infants with abnormal repeated scans.

Cranial ultrasound begins with grayscale imaging of the brain using a sector transducer via the anterior fontanel. The GE Logiq E9 ultrasound equipment with linear 5 to 7 MHz probe was used. In the coronal plane, images are obtained from anterior to posterior, beginning at the frontal lobes just anterior to the frontal horns of the lateral ventricles and extending to the occipital lobes posterior to the lateral ventricles. Imaging in the sagittal plane begins with a midline sagittal view that includes the corpus callosum, third and fourth ventricles, brain stem, and cerebellar vermis. Sequential images are then obtained through the right and left cerebral hemispheres, respectively, sweeping through the lateral ventricles, periventricular white matter, and peripheral cortex to the Sylvain fissures. All antiseptic precautions were taken, and sterilized ultrasound gel was used. Precaution was taken to avoid undue pressure of the probe on the fontanel.

Statistical analysis

The information was analyzed using STATA/MP12 (StataCorp LP, College Station, TX, USA). General information of the patients was described using descriptive statistics as number, percentage, average, standard deviation, minimum and maximum value. The comparison was made using chi-square test or Fisher's exact test for a categorical data, and independent t-test and Mann-Whitney U test for continuous data. To evaluate the appropriate number for repeating the head ultrasound test, positive predictive values, negative predictive values, sensitivity, and specificity were used. A probability value of less than 0.05 was considered significant.

Ethical consideration

The present study was performed in a retrospective basis. No patients were requested to receive any further intervention. The analyses of the data were performed without recording the patients' names or any personal information.

Results

During the study period, 133 neonates with GA of less than 32 weeks were admitted to NICU of Phramongkutklao Hospital. One hundred eight were screened by the cranial ultrasound tests. An IVH was found in 24 infants (22.2%). For the 25 neonates who had no HUS, 11 neonates died before any scan was done and all these 25 neonates were excluded from the analyses.

Table 1. Abnormalities found on the first HUS

Findings	Number of cases
Cyst	2
Grade I intraventricular hemorrhage	11
Grade II intraventricular hemorrhage	4
Grade III intraventricular hemorrhage	1
Grade IV intraventricular hemorrhage	1
Periventricular leukomalacia (PVL)	1
Ventriculomegaly (VM)	1

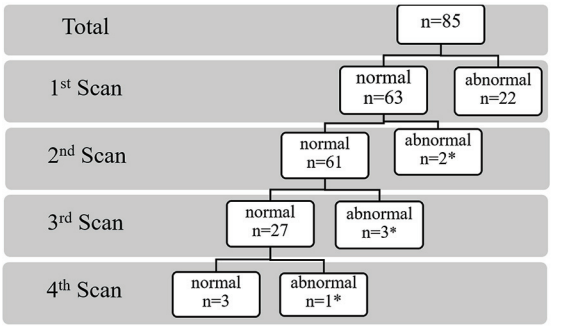

Figure 1. Number of abnormalities found after each HUS.

* 5/6 of HUS showed cysts and 1/6 of HUS showed ventriculomegaly

Twenty-three infants had only one scan, 16 of 23 had normal findings, whereas the others had abnormal findings. Among the seven neonates who had abnormal screening since the first scanning but did not go on further HUS, almost all (6/7 or 85.7%) died. The other was followed up using computed tomography (CT) scan instead of HUS.

Eighty-five neonates had more than one HUS. The first date of HUS ranged between day 1 to day 39 of life with a mean and median of 4.4 days and 2 days, respectively. After the first screening, 63 out of 85 found no abnormality. The remaining 22 neonates had abnormal finding. The abnormalities are listed in Table 1. Timing of detecting the abnormality ranged from 1 to 39 days of life with a mean and median of 6 days and 2 days, respectively.

Of the remaining 63 neonates who had normal first screening, 61 (96.8%) went on the second screening during the 3rd to 131st day of life (mean 19.2 days, median 10 days) and abnormalities were found in two out of 61 neonates (3.3%), which were cysts and found on day 7 and day 30 of life.

The remaining 61 neonates who their first two HUS were all normal, only 30 went on the third screening and most of them (27/30 or 90.0%) still had normal findings. The positive findings of the other three neonates were cysts (n=2) and ventriculomegaly (n=1).

Finally, the remaining 27 neonates who had normal first three HUS, only four went on the fourth screening, which showed no abnormality in three out of four. The one with abnormality had cyst, which was found on day 90 of life. This neonate also went on the fifth HUS and no change was found. The number of neonates with normal and abnormal findings after each HUS is listed in Figure 1.

In conclusion, the number of missed diagnosis with single HUS was six out of 63 or 9.5%. Among these six neonates, five abnormalities were cysts and the other was ventriculomegaly. All the neonates and their HUS findings are summarized in Figure 2.

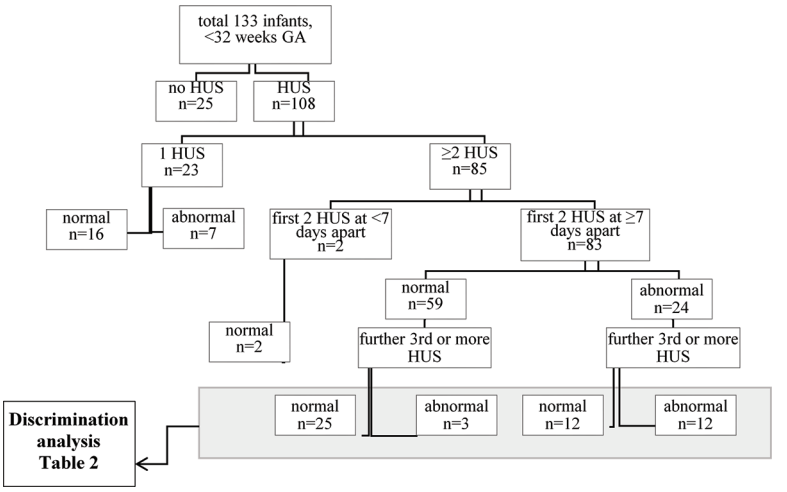

Figure 2. Population of neonates.

Table 2. Infant with two normal HUS studies ≥7 days apart

Variables	No subsequent (n=31) n (%)	Subsequent (n=28) n (%)	p-value*
Sex			0.243
Male	13 (41.94)	16 (57.14)	
Female	18 (58.06)	12 (42.86)	
GA; mean±SD	29.16±1.66	28.79±1.97	0.043
BW; mean±SD	1,341.1±282.04	1,121.54±341.08	0.009
LOS; mean±SD	48.1±24.37	69.86±36.94	0.011
Delivery			0.779
C/S	21 (67.74)	18 (64.29)	
Vagina	10 (32.26)	10 (35.71)	
DOL1; mean±SD	4.74±4.94	2.96±1.82	0.069
DOL2; mean±SD	24.52±33.83	14.46±9.95	0.123

GA=gestational age; BW=birth weight; LOS=length of stay; C/S=cesarean section; DOL=day of life; SD=standard deviation

* Chi-square test and independent t-test

Of the 59 infants who had two normal HUS studies at 7 or more days apart, 28 had additional follow-up evaluations, while 31 did not. The 28 infants who had subsequent HUS studies had a lower BW and longer hospital stay compared to the other group (Table 2).

As shown above, in the group of neonates having repeated scans, 25 out of 28 (89.3%) still had normal scan, whereas three neonates became abnormal. These three infants were all clinically unstable and two had respiratory distress syndrome (RDS) requiring surfactant while the other had transient tachypnea. All of them received antibiotics for the suspected sepsis, presence of metabolic imbalance, and pathologic jaundice.

The discrimination analysis demonstrated that two normal HUS studies at 7 or more days apart predicted subsequently normal studies with a sensitivity of 67.6%, a specificity of 80%, and a positive predictive value of 89.3% (p=0.002) (Table 3).

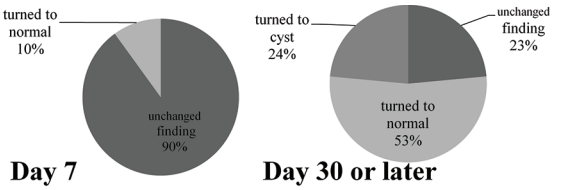

Figure 3. The percentage of finding change.

Regarding the IVH rate, among 85 patients with at least 2 HUS, 24 had IVH (31.8%). Of the 24 preterm infants with IVH, only 19 cases repeated the cranial ultrasounds. Four out of six infants died before repeating the HUS. Among 10 infants who repeat HUS early (day 7 or earlier), no change in finding was found in nine infants and the other one, grade I-IVH resolved to normal. If the repeat HUS was done on day 30 or later, the findings were changed in most cases (13/17 or 76.4%) and only four infants had unchanged findings (Figure 3).

Discussion

Regarding to the proper number of cranial ultrasound screening in preterm infants, the present study demonstrated that the vast majority of abnormalities detected from cranial ultrasound screening are usually found on the first screening at median of 2 day-old with 25.8% (22/85). While two to four additional scans were performed in the previously normal cases, only a few new findings were found. More importantly, the new findings found from the subsequent scans tended be "slightly abnormal" requiring no further treatment or intervention (5/6=cyst and 1/6=ventriculomegaly). Furthermore, although the neonates who went on subsequent scans were significantly poorer in prognosis (significantly lower BW and longer LOS), they still had no difference in subsequent scan finding. While some significant findings tended to be detectable earlier, some findings were detected late only in the subsequent scans. The possible explanation is that the pathophysiology of some conditions, such as cysts,

Table 3. Discrimination analysis for two normal HUS studies ≥7 days apart predicting a normal third HUS subsequently

No. of normal scan	Normal	Abnormal	
2 normal scans	25	3	PPV 89.3% (95% CI 71.8 to 97.7)
1st or 2nd normal scan	12	12	NPV 50.0% (95% CI 29.1 to 70.9)
	Sensitivity 67.6% (95% CI 50.2 to 82.0)	Specificity 80.0% (95% CI 51.9 to 95.7)	

PPV=positive-predictive value; NPV=negative-predictive value; CI=confidence interval

Chi-square test, p=0.002

needs time to occurred.

According to the discrimination analysis, most neonates (89.3%) who have had two normal HUSs at 7 or more days apart tended to have normal repeat studies. These findings were consistent with those reported by Nwafor-Anene et al[4] in which 94% of infants lighter than 1,500 g at birth who had two normal or slightly abnormal HUS studies at three to five days of life and again at 10 to 14 days, had subsequently normal studies. The sensitivity, specificity, and PPV found were 94%, 86% and 94%, respectively, which were comparable to the present study at 67.6%, 80%, and 89.3% (p=0.002), respectively.

Regarding the incidence of IVH (31.8%), it was in concordance with previously reported (45% to 65%)[5-7]. Among the neonates with IVH who had subsequent scan, it was found that repeating scan at day 7 resulted in finding change in only 10%. Whereas, repeating the scan at day 30 or later resulted in change in finding of as high as 76.4%. These findings may be due to a slow-progression nature of the disease. However, to skip repeating the scan at day 7 may delay diagnosis and treatment, thus, these data needed to be confirmed in a future prospective study. Furthermore, this data may lead to making the guideline of care for preterm neonates in Thailand where pediatric radiologists are always in shortage and the cost of HUS is still a problem. Therefore, the authors' may skip repeating the scan at day7 for known-case IVH. In addition, repeating the HUS at day 30 or later seemed to be reasonable.

However, there were some limitations of the present study. First, the study was a retrospective study, ultrasounds were performed by many physicians including both pediatricians and radiologist that may affected the result of the scans. Secondly, the data about clinical correlation was incomplete. Some neonates who showed normal finding from HUS may be a false negative. Last, the value of additional HUS may be underestimated due to preterm neonatal care. Some of neonates who had no repeat scans died, and the number of infants included in the study were small.

Conclusion

Routine screening with cranial ultrasound is recommended for all infants born younger than 32 weeks GA at very first day of life. If the scan is abnormal, repeating the scan at day 30 or later may be more reasonable than as early as day 7. However, if the scan showed no abnormality and is repeated at day 7 or later with the same negative result, subsequent scan may not provide benefits. However, these findings need to be proved and may be used as a guide to design a future prospective study.

What is already known on this topic?

Routine screening with cranial ultrasound is recommended for all infants younger than 32 weeks GA and should be repeated according to GA and BW.

What this study adds?

If the scan was abnormal, repeating the scan at day 30 or later may be more helpful than as early as day 7. However, if the scan showed no abnormality and had been repeated at day 7 or later, with the same negative result, subsequent scan may not provide any additional benefits.

Conflicts of interest

The authors declare no conflict of interest.

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