Surveillance Protocol for the Detection of Intracranial Abnormalities in Premature Neonates

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Objective: To determine the optimal timing of cranial ultrasound scans (USs) for identifying preterm neonates weighing less than 1500 g at birth who develop intracranial complications of prematurity.

Design/Setting: Observational study at an urban county hospital.

Methods: Serial USs from neonates with less than 1500-g birth weight (BW) admitted to the neonatal intensive care unit between January 1995 and December 1996 were reviewed by a pediatric neuroradiologist in a blinded random manner.

Results: Two hundred forty-eight neonates (78%) underwent at least 3 USs, 32 (10%) had 2 USs and 37 (12%) only 1 US. The initial US was normal in 156 neonates (49%) and abnormal in 161 (57%). The principal abnormalities included intraventricular hemorrhage (IVH) (n=74), periventricular echogenicity (PVE) (n=68), ventriculomegaly (n=7), and solitary cysts (n=9). Severe IVH (n=17) occurred in 13 (11.4%) of 114 neonates at less than 1000-g BW and 4 (5%) of 79 neonates of BW 1000 to 1250 g. In 11 cases (65%), the severe IVH was clinically unsuspected. For neonates weighing less than 1000 g, IVH was diagnosed by days 3 to 5 in 10 (77%) of 13, by days 10 to 14 in 11 (84%) of 13, and by day 28 in all neonates; for neonates 1001 to 1250 g, IVH was diagnosed in 1 (24%) of 4 by days 3 to 5, 2 (50%) of 4 by days 10 to 14, and 3 (75%) of 4 by day 28. One infant's condition was diagnosed on routine US before discharge from the hospital. Cystic periventricular leukomalacia (PVL) was noted in 9 neonates; in 4 of the 9 cases, increased PVE was present on the initial US and cyst formation was obvious by the second US. For 4 neonates (3 with BW <1000 g), all routine USs were negative and cystic PVL was noted on the pre-discharge US in these cases. Nonobstructive ventriculomegaly in the absence of IVH or cystic PVL was observed in 14 neonates. In 6, it was noted on the initial screening US; in 4 of the cases, it evolved after the third screening US. Two hundred fifty-six neonates had a US before discharge from the hospital; 181 (72%) were normal and 75 (28%) abnormal. Nine significant lesions were identified by the US before discharge from the hospital (ie, severe IVH [n=1], cystic PVL [n=4], and ventriculomegaly [n=4]).

Conclusions: The following screening protocol is recommended: (1) Neonates of less than 1000-g BW: initial US on days 3 to 5 (should identify at least 75% of cases of IVH and some PVE abnormalities); second US on days 10 to 14 (should detect at least 84% of IVH and identify early hydrocephalus and early cyst formation); third scan on day 28 (should detect all cases of IVH, as well as assess PVE and ventricular size); and final scan before discharge from the hospital (should detect approximately 20% of significant late-onset lesions). (2) Neonates of 1000- to 1250-g BW: initial US at days 3 to 5 (should detect at least 40% of significant abnormalities); a second scan at day 28 (should detect at least 70% of significant abnormalities); and a predischarge scan (should detect all late-onset significant lesions). (3) Neonates of 1251- to 1500-g BW: an initial scan at days 3 to 5; and a second scan before discharge from the hospital if the clinical course is complicated.


CRANIAL ultrasound scans (USs) are widely used to identify preterm neonates at risk for brain injury and subsequent neurodevelopmental defects, most commonly as a consequence of severe intraventricular hemorrhage (IVH) and cystic periventricular leukomalacia (PVL). Intraventricular hemorrhage occurs in 40% of premature neonates who weigh less than 1500 g; 90% of hemorrhages occur within the first 3 postnatal days and the remainder by 10 days. Intraventricular hemorrhage is usually clinically occult, and detection requires a screening US. Periventricular leukomalacia is seen in 3% to 10% of premature neonates. The sonographic criteria of PVL are increased white matter echogenicity that evolves to cyst formation. However, clinically significant white matter injury may occur without frank cyst formation and in the absence of white matter changes on US, as evidenced by development of nonobstructive ventriculomegaly not associated with...
SUBJECTS AND METHODS

The study population was derived from 379 neonates with birth weight (BW) of less than 1500 g delivered at Parkland Memorial Hospital, Dallas, Tex, and admitted to the Neonatal Intensive Care Unit between January 1995 and December 1996. Fifty neonates (13%) died within 24 hours from extreme prematurity or other medical conditions and did not undergo a cranial US. In 12 other neonates (3.1%), cranial USs was not performed. Thus, cranial USs were available for review on the remaining 317 neonates.

SCREENING PROTOCOL

The long-standing screening protocol in our institution for preterm neonates of less than 1500-g BW includes USs on days 3 to 5, 10 to 14, 28, and/or before discharge from the hospital (hereafter referred to as predischarge). Scans are also obtained more frequently as clinically indicated; these are not considered screening examinations. Standard coronal and parasagittal images are obtained with an Acuson 128 XP ultrasonographic scanner (Acuson, Mountain View, Calif) using a 7.5-mHz transducer through the anterior fontanel. The USs were prospectively interpreted by 5 pediatric radiologists on a rotating basis as part of standard practice. The results were entered into a database and coded based on the definitions outlined in Table 1.

Ultrasound studies from 150 of these neonates were submitted for review to a pediatric neuroradiologist (N.R.); the images were reviewed in a blinded random manner, not in sequential order, and without knowledge of the results of the previous or subsequent USs. The studies included screening as well as clinically indicated scans and included the cases of severe IVH and its complications, PVL, ventriculomegaly, solitary cysts, some of the cases of lesser grades of IVH and transient periventricular echogenicity (PVE), and 50 normal cases. The BW and gestational age (GA) (as assessed using the modified Ballard measure13) were also recorded in the database.

STATISTICS

Data were analyzed by t test where appropriate. All data are presented as mean ± SD unless otherwise stated.

IVH. Because of the sensitivity of USs to IVH and periventricular abnormalities and the ease with which USs can be performed at the bedside, surveillance protocols using USs have evolved for screening premature neonates. In recent years, the incidence of all grades of hemorrhage has decreased because of increased antenatal steroid use and improved neonatal care. As cost containment has become a more pressing issue, the need and frequency of screening USs has been raised. The objective of this analysis was to determine the optimal timing of cranial USs scanning for identifying pre- term neonates weighing less than 1500 g who develop intracranial complications of prematurity.

RESULTS

Two hundred forty-eight neonates (78%) underwent at least 3 USs, 32 (10%) had 2 USs, and 37 (12%) underwent only 1 US. Neonates who were scanned less frequently were larger (ie, 1329±141 g vs 1096±268 g [P = .0001]) than neonates scanned frequently. The initial US obtained on day 3 (range, 1-5 days) was abnormal in 161 neonates (51%) and normal in 156 (49%). The abnormalities included the following: IVH (n=74) (grade 1, 38 neonates; grade 2, 26 neonates; grade 3 and/or intraparenchymal echogenicity (PVE), 10 neonates); increased PVE (68 neonates); ventriculomegaly (7 neonates); solitary cysts (9 neonates) (choroid plexus, 5 neonates, and germinal matrix, 4 neonates); congenital hydrocephalus (1 neonate); lissencephaly (1 neonate); and increased cerebellar echogenicity (1 neonate). No neonate had cystic PVL on the initial scan. The specifics of neonates with severe IVH, cystic PVL, and ventriculomegaly are outlined below.

SEVERE IVH

Severe IVH occurred in 17 neonates (5.3%) with a BW, of 799±184 g, and a GA of 25.3±1.53 weeks. Thirteen (11.4%) of 114 neonates of less than 1000-g BW and 4 (5%) of 79 neonates from 1000- to 1250-g BW. In 11 (65%) of 17 neonates, the IVH was clinically unsuspected. For neonates of 1000-g BW, IVH was diagnosed by days 3 to 5 in 10 (77%), days 10 to 14 in 11 (84%), and day 28 in all 13 cases (Table 1). For neonates of

<table>
<thead>
<tr>
<th>Table 1. Definition of Cranial Ultrasound Abnormalities*</th>
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<tr>
<td>Intraventricular hemorrhage</td>
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<tr>
<td>Grade 1: Blood confined to the germinal matrix region</td>
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<td>Grade 2: Blood filling &lt;50% of the lateral ventricle on sagittal view</td>
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<tr>
<td>Grade 3: Blood filling &gt;50% of the lateral ventricle with distention on sagittal view</td>
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<td>IPE: Increased echogenicity (of greater intensity than the choroid plexus) located in periventricular white matter observed on both coronal and sagittal views†</td>
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<td>Periventricular leukomalacia</td>
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<td>Postnatal evolution of cysts within periventricular white matter in the presence or absence of prior hyperechogenicity</td>
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<td>Transient periventricular hyperechogenicity</td>
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<td>Increased PVE (of greater intensity than the choroid plexus) that resolves without cyst formation or the evolution to ventriculomegaly on subsequent scans</td>
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<tr>
<td>Ventriculomegaly</td>
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<tr>
<td>Appearance of dilated lateral ventricles, limited to the frontal horns and atrial trigones, in the absence of intraventricular hemorrhage</td>
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<tr>
<td>Solitary cysts</td>
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<tr>
<td>Appearance of solitary cysts within the germinal matrix or choroid plexus</td>
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<tr>
<td>Linear thalamic echogenicity</td>
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<td>Appearance of linear echoes within the thalamus or basal ganglia</td>
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*PVE indicates intraparenchymal echogenicity; IVH, intraventricular hemorrhage; and PVE, periventricular echogenicity. †Often referred to as grade 4 IVH. Severe IVH was referred to as grade 3 and/or IPE.
1001- to 1250-g BW, IVH was diagnosed by days 3 to 5 in 1 (25%), days 10 to 14 in 2 (50%), and day 28 in 3 (75%) of 4 cases. One infant with a grade 1 hemorrhage on day 28 was diagnosed as having a grade 3 IVH on a routine US obtained predischarge. Two neonates (11%) developed posthemorrhagic hydrocephalus during the first postnatal month, ultimately requiring ventricular decompression.

### CYSTIC PVL

Cystic PVL developed in 9 (2.8%) of the 317 neonates (Table 2). These neonates were larger (BW, 970±228 g) and more mature (GA, 27.2±1.83 weeks) than neonates with severe IVH (P<.01). Six of the 9 neonates were of less than 1000-g BW. In 2 of the 6 cases, increased PVE were observed on the initial US and cyst formation was already obvious by the second US. One infant with a grade 1 hemorrhage on day 28 was diagnosed as having a grade 3 IVH on a routine US obtained predischarge. Two neonates (11%) developed posthemorrhagic hydrocephalus during the first postnatal month, ultimately requiring ventricular decompression.

### VENTRICULOMEGALY

Fourteen neonates with a BW of 918±192 g and a GA of 26.7±1.9 weeks had ventriculomegaly without IVH or cystic PVL (Table 3). The ventriculomegaly varied from mild to moderate and was limited to the frontal horns and atrial trigones of the lateral ventricles (Figure). Seven neonates had ventriculomegaly on the initial screening US. In 2 of 7, the ventriculomegaly resolved by the third US or day 28. By day 28, 3 additional neonates had developed ventriculomegaly. Thus, 8 neonates had nonobstructive ventriculomegaly by day 28. Four additional neonates had ventriculomegaly on a predischarge sonogram. Thus, 12 neonates had ventriculomegaly at the time of discharge from the hospital (Table 4). In 10 of 12 cases, the ventriculomegaly was bilateral, and in 2 cases, unilateral.

### DISCHARGE US

Twenty-one neonates died during hospitalization; 37 neonates had a single US performed during hospitalization, and 3 neonates were transferred to a secondary hospi-
tal. Thus, 256 neonates had a predischarge US. The predischarge US was normal in 181 neonates (72%) and abnormal in 75 (28%). The abnormalities included resolving IVH (n = 31) and late-onset clinically occult IVH (n = 5) (ie, grade 1 IVH, 4 neonates; grade 3 IVH, 1 neonate; hydrocephalus/porencephaly (n = 5); ventriculomegaly (n = 12); PVL (n = 9); solitary cysts (n = 5); and new-onset PVE (n = 2). Thalamic echoes, either as isolated phenomena or in association with one of the above abnormalities, developed in 10 neonates.

**Significant Lesions Identified by a Predischarge US**

Nine significant abnormalities (ie, severe IVH [1 neonate], cystic PVL [4 neonates], and ventriculomegaly [4 neonates]) were detected by the predischarge US. The ventriculomegaly was bilateral in 3 and unilateral in 1 case (Table 5).

**Comparison of Prospective and Retrospective US Interpretations**

The overall concordance between prospective interpretation and the review of the 150 US studies was 98%. Discrepancies in interpretation related to the conspicuousness and significance of white matter echogenicity.

The data in this report indicate that up to 50% of neonates weighing less than 1500 g exhibited some abnormality on the initial US, although abnormalities considered to be of clinical significance occurred in less than 5% and were seen only in the smallest neonates. Severe IVH was observed in approximately 11% of the neonates weighing less than 1000 g and in 5% of those between 1000- and 1250-g BW. Cystic PVL was noted in 5% of the neonates weighing less than 1000-g and in approximately 1% of those between 1250 and 1500 g. Ventriculomegaly in the absence of IVH, considered to be a marker of occult white matter injury, was noted in 7% of neonates of less than 1000-g BW. The overall incidence of these abnormalities is consistent with previous reports. However, the timing or evolution of these lesions seems to be changing. Previous studies have indicated that most cases of severe IVH (>90%) occur in the first 3 days of life, whereas, in this report, approximately 65% of the cases were detected within the first week. The remaining cases were detected in the second or third postnatal week; 1 infant developed severe IVH after day 28. Cystic PVL also tended to occur later and often in the absence of prior sonographic abnormalities. This is consistent with some previous observations but is in conflict with other studies, which indicate that most cases of cystic PVL are heralded by prior hyper-echogenicity in the early postnatal period. The onset of ventriculomegaly was more varied. In 50% of neonates, ventriculomegaly was present on the initial US, whereas in the remaining cases, the ventricles enlarged over time; in 25% of the latter cases, ventriculomegaly only became apparent after day 28. Recent data indicate the importance of ventriculomegaly as an independent predictor of adverse neurodevelopmental outcome.

Although 50% of neonates had an abnormal initial US, 72% of these were interpreted as normal by the time of discharge from the hospital. Of the approximately 30% of neonates with an abnormal predischarge US, the abnormalities were severe in 9 cases (12%), and only detected on the predischarge US.

The observations in this report may provide a basis for making recommendations regarding the frequency and timing of screening USs in high-risk premature neonates. However, any screening protocol needs to take into account that most intracranial pathologic processes in the sick premature neonate is clinically occult, that severe lesions occur most often in the tiniest of premature neonates, and that there seems to be a shift toward a delayed presentation of the clinically more significant lesions. Based on the above observations, we would recommend that screening USs be performed as follows: for neonates of less than 1000-g BW, an initial screening US should be obtained on days 3 to 5; this should identify at least 75% of cases of IVH and may identify early periventricular white matter abnormalities. A second US on days 10 to 14 should detect most cases of IVH and identify early hydrocephalus. Early cyst formation within white matter may also be apparent at this time. We would recommend a third scan on day 28. This should detect almost all cases of severe IVH and assess periventricular white matter and ventricular size. Given the unexpectedly high yield of significant sonographic abnormalities (ie, 20% noted on the predischarge US), we consider a predischarge US is indicated in all neonates of less than 1000-g BW. For neonates of 1001-1250-g BW, we recommend a screening US on days 3 to 5, which should detect at least 40% of significant lesions; a second scan at day 28, which should detect at least 70% of significant lesions; and a final predischarge US. For neonates between 1250- and 1500-g BW, we recommend a US on days 3 to 5 and a second scan before discharge from the hospital if the clinical course is complicated in any way. Scans should obviously be obtained more frequently as clinically indicated for all BW categories. This reduction in frequency of screening USs in the relatively “larger high-risk neonate” (ie, >1000 g) (for our population, this approximates 300 per year) should not reduce the ability to detect significant neuropathologic processes even in the absence of clinical symptoms, and should, at the same time, address the concerns of cost containment (ap-

| Table 5. Severe Intraventricular Hemorrhage, Cystic Periventricular Leukomalacia, and Ventriculomegaly by Screening Cranial Ultrasound (US) as a Function of Birth Weight |
|-----------------|-----------------|-----------------|-----------------|-----------------|
| Birth Weight, g | Screening US at Postnatal Age in Days, No. (%) | | | |
| | 3-5 | 10-14 | 28 | Predischarge |
| <1000 (n=25) | 13 (52) | 16 (64) | 20 (80) | 25 (100) |
| 1001-1250 (n=10) | 4 (40) | 5 (50) | 7 (70) | 10 (100) |
| 1251-1500 (n=5) | 1 (20) | 3 (60) | 4 (80) | 5 (100) |

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proximately $30000 per year in our institution). Clearly, these issues can only be definitively addressed in a prospective randomized study.

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REFERENCES