ABSTRACT. Real-time ultrasound scans were performed on 66 low-birth-weight infants within the first six hours of life (mean, two hours), and then at 12, 24, 48, and 72 hours, and thereafter at weekly intervals. All of the infants were born in a perinatal unit. The incidence of intraventricular hemorrhage and subependymal hemorrhage was 31%. Eight of 20 infants had small hemorrhages (Papile, grades I and II); seven infants sustained grade III hemorrhages, and five infants sustained grade IV hemorrhages. All hemorrhages occurred in the first 72 hours of life; 25% were diagnosed with the first scan (ie, within the first six hours of life). The infants especially at risk were those less than 29 weeks' gestation. Five infants developed progressive posthemorrhagic ventriculomegaly that subsided spontaneously by age 8 weeks. The mortality in the study group was only 4.5%. Pediatrics 1983;71:541-546; intraventricular hemorrhage, subependymal hemorrhage, low-birth-weight infants.

The reported incidence of intraventricular hemorrhage (IVH) in infants with birth weight <1,500 g, as detected by computed tomography (CT) scanning is 43%. Real-time ultrasound studies have demonstrated an incidence of between 46.7% to 90%. However, in the latter study, only half of the hemorrhages were of a major degree.

It has been shown that neonatal survival and long-term outcome can be improved by delivering low-birth-weight infants in a perinatal unit. It has also been demonstrated that the incidence of IVH/subependymal hemorrhage (SEH) is much lower when infants are born in a perinatal setting.

Intracranial hemorrhage, apart from subarachnoid hemorrhage, can be detected in the preterm infant, with real-time ultrasound. The definition of the time of occurrence of SEH/IVH is crucial to an understanding of etiologic factors, in order that these lesions may be prevented. The events preceding hemorrhage need to be separated from the signs and symptoms that result from the hemorrhage itself. Real-time ultrasound scanning is a sensitive and noninvasive method of detecting SEH and IVH, and for the detection of intraparenchymal extension of hemorrhage and posthemorrhagic ventricular dilation.

In this study, we report the incidence and severity of SEH/IVH in a group of low-birth-weight infants delivered in a regional perinatal unit, the time of occurrence of such hemorrhages, and the correlation of postnatal factors with the timing of these hemorrhages.

PATIENTS AND METHODS

Sixty-six newborn infants of less than 32 weeks' gestation or <1,500 g birth weight, born consecutively in the Regional Perinatal Unit of Women's College Hospital, Toronto, between August 1981 and January 1982, were studied prospectively.

Intraventricular hemorrhage or subependymal hemorrhage was detected by a portable ATL (Advanced Technology Mark III) real-time sector scan-
ner with a 5-MHz transducer. Images were obtained through the anterior fontanel in both right and left parasagittal, coronal, and axial planes, with the infants lying in an isolette within the neonatal intensive care unit. First a “sweep” was recorded on video tape and subsequently individual images were obtained in each plane.

The first ultrasound scan was obtained within six hours of delivery (mean age, 2 hours). Studies were repeated at 12, 24, 48, and 72 hours, 1 week, and 1 month of age. If indicated clinically, the scan was repeated at any time. Infants who sustained pneumothorax received a repeat ultrasound scan after stabilization. If SEH or IVH was detected, the scans were repeated at weekly intervals until hospital discharge. The hemorrhages were graded by the classification of Papile and associates1: grade I, hemorrhage confined to germinal layer matrix; grade II, intraventricular hemorrhage; grade III, intraventricular hemorrhage with ventricular dilation; grade IV, intraparenchymal hemorrhage.

Examples of each grade of SEH/IVH are shown in Fig 1. SEH was diagnosed when a focal, echodense collection was seen in the region of the caudate nucleus in both the coronal and parasagittal scans.

Clinical information was recorded daily, by a neonatologist or research nurse. Statistical analysis was undertaken by $x^2$ and Student $t$ test as indicated. $P$ values < .05 were considered significant. Cord blood gases were obtained in every case by sampling directly from an umbilical vessel after double clamping the cord at delivery. Gestational age was assessed using the criteria described by Dubowitz et al11 in conjunction with the antenatal history.

RESULTS

The study group comprised 64 infants. During the study, 66 newborns were investigated; however, two were excluded when they died at 12 and 24 hours of age, respectively, from causes unrelated to SEH or IVH: one infant had multiple congenital abnormalities and the other died from massive pulmonary hemorrhage. It was determined that neither infant had suffered SEH/IVH.

The total incidence of IVH and SEH was 31% (20/64), but only 19% of the total had severe hemorrhages (grade III and IV). The distribution of SEH/IVH by grades is presented in Table 1.

The overall mortality in the study group was 4.7% (3/64), the case fatality rate of infants with SEH/IVH was 15% (3/20). In only one of these infants was death associated with extension of the hemorrhage into the cerebral tissue. Five infants with grade III and IV hemorrhages developed progressive posthemorrhagic ventriculomegaly. None of these infants, however, required treatment.

All hemorrhages occurred in the first 62 hours of life, and increase in size of the hemorrhage after 72 hours of age, occurred in only three cases. The distribution of IVH and SEH by the time of occurrence is shown in Fig 2. There was no significant statistical relationship between the time of detection of hemorrhage and its severity, or presence or absence of perinatal asphyxia as judged by Apgar scoring, cord pH, or cord PCO$_2$ (Table 2). Of the 64 premature newborns, 26 were between 30 and 34 weeks' gestation, and of these, only two had ultrasound findings that were abnormal: one infant had an SEH and the other had a grade IV IVH. The distribution of SEH/IVH according to gestational age is presented in Fig 3. There was a significant difference between the incidence of SEH and IVH in infants whose gestational age was less than or equal to 29 weeks and infants between 30 and 34 weeks' gestational age ($P < .01$). Among infants less than 29 weeks' gestational age 56% had SEH or IVH which was diagnosed within the first 24 hours. (Fig 4).

All infants received aggressive resuscitation and immediate ventilatory support. The incidence of hyaline membrane disease was only 15%, and the distribution of hyaline membrane disease was similar in infants, both with and without SEH/IVH. The incidence of pneumothorax was 14% and there was no significant difference in its occurrence between the two groups. Of four babies in the SEH/IVH positive group who developed pneumothorax, three sustained the hemorrhage eight to 36 hours after the pneumothorax was drained. Other postnatal factors in both groups are presented in Table 2.

In the group with SEH/IVH, the diagnosis was suspected on clinical grounds in only 30% of the cases. The criteria for clinical suspicion of SEH/IVH included unexplained decrease in hematocrit level associated with fullness of the fontanel, change in neurologic status (especially a change in tone or activity, including the presence of seizure

Fig 1. Coronal (left) and parasagittal (right) sonograms through anterior fontanel: A and B, grade I hemorrhage: right subependymal hemorrhage (SEH) (arrows); choroid plexus (c); C and D, grade II hemorrhage: blood clot (arrows) in occipital horn of normal-sized left lateral ventricle; choroid plexus (c); E and F, grade III hemorrhage: subependymal hemorrhage (S), intraventricular clots (H), and marked dilatation of lateral ventricles (v), choroid plexus (c); G and H, grade IV hemorrhage: SEH has extended into brain parenchyma on right (arrows).
As defined by Papile et al.\textsuperscript{1}

TABLE 1. Distribution of 20 Cases of Subependymal (SEH)/Intraventricular Hemorrhage (IVH) by Grades*  

<table>
<thead>
<tr>
<th>Grade of SEH/IVH</th>
<th>Survived</th>
<th>Died</th>
</tr>
</thead>
<tbody>
<tr>
<td>SEH, grade I</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>IVH without ventricular enlargement, grade II</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>IVH with ventricular enlargement, grade III</td>
<td>7</td>
<td>0</td>
</tr>
<tr>
<td>SEH with cerebral extension, grade IV</td>
<td>4</td>
<td>1</td>
</tr>
</tbody>
</table>

* As defined by Papile et al.\textsuperscript{1}

Fig 2. Distribution of subependymal hemorrhage (SEH) and intraventricular hemorrhage (IVH) by time of occurrence.

TABLE 2. Postnatal Factors Associated with Occurrence of Subependymal Hemorrhage (SEH)/(IVH)*  

<table>
<thead>
<tr>
<th>Factor</th>
<th>Hemorrhage (N = 20)</th>
<th>Nonhemorrhage (N = 44)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight Mean ± SD</td>
<td>1,142 ± 230</td>
<td>1,244 ± 335</td>
</tr>
<tr>
<td>Range</td>
<td>870-1,500</td>
<td>550-2,600</td>
</tr>
<tr>
<td>Sex: M/F</td>
<td>8/12</td>
<td>23/21</td>
</tr>
<tr>
<td>Apgar 1 min (mean ± SD)</td>
<td>5.1 ± 2.5</td>
<td>6.0 ± 2.13</td>
</tr>
<tr>
<td>Apgar 5 min (mean ± SD)</td>
<td>7.1 ± 1.65</td>
<td>8.0 ± 1.18</td>
</tr>
<tr>
<td>Apgar &lt;5 at 1 min</td>
<td>10</td>
<td>17</td>
</tr>
<tr>
<td>Apgar &lt;5 at 5 min</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Cord pH (mean ± SD)</td>
<td>7.33 ± 0.07</td>
<td>7.33 ± 0.06</td>
</tr>
<tr>
<td>Cord Pco2 (mean ± SD)</td>
<td>38 ± 6.22</td>
<td>40 ± 9</td>
</tr>
<tr>
<td>Pneumothorax</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>Patent ductus arteriosus</td>
<td>4</td>
<td>8</td>
</tr>
</tbody>
</table>

* In all factors, findings were not significant.

activity), and persistent metabolic acidosis. Conversely, in the nonhemorrhagic group, 26% were wrongly suspected of having sustained SEH/IVH on the basis of clinical criteria.

DISCUSSION

The incidence of SEH and IVH in a mixed inborn and outborn population varies between 43% and 46.7%.\textsuperscript{1,2} Clark et al.\textsuperscript{7} found a significant difference between inborn and outborn newborns; the incidence of SEH/IVH was 56% in the outborn and only 12% in the inborn population. The severity of the hemorrhage was also less in the inborn population in which grade III and IV hemorrhages occurred in only 6%, compared with 33% in the outborn group.

This study was done in a perinatal center, where a staff neonatologist together with a pediatric resident and neonatal intensive care nurse, performed the resuscitation in each preterm infant. The incidence of severe hemorrhages (grades III and IV) was only 19%, and the overall incidence of SEH/
IVH was 31%. Posthemorrhagic hydrocephalus develops due to obstructive arachnoiditis, and the severity of the arachnoiditis is directly related to the amount of blood that flows downward through the aqueduct into the fourth ventricle, and escapes to the area of the cisterna magna and subarachnoid space. Ahmann et al. reported a 26% incidence of hydrocephalus in infants with IVH who were less than 35 weeks' gestation. Several studies have shown a relationship between the degree of posthemorrhagic ventriculomegaly and the severity of the IVH. Of the 12 infants in our study, who sustained grade III or IV hemorrhages, only five developed progressive posthemorrhagic ventriculomegaly, and all were observed until repeat ultrasonographic imaging had demonstrated a decrease in ventricular size. All ventriculomegaly had partially resolved by 8 weeks of age, and none required a shunting procedure.

The overall case fatality rate for infants in our study with SEH/IVH was 15%, whereas Papile et al. reported a mortality of 55% in low-birth-weight infants with SEH/IVH. The distribution of severity of hemorrhage in the two groups was identical, and the only differences between the groups were that ours was a completely inborn population and all of our infants received immediate ventilatory support.

In a prospective study, using CT scanning for the diagnosis of IVH, Lazzara et al. found that 81% of the severe hemorrhages and only 30% to 36% of mild or moderate hemorrhages were suspected clinically. In our study group only 30% of cases of SEH/IVH were suspected clinically. This observation is consistent with the lower incidence of severe hemorrhage in our population.

To program clinical trials for prevention of intraventricular hemorrhage, it is of major importance to delineate the timing of occurrence and the population at risk and to assess etiologic factors involved in pathogenesis.

To determine the timing of hemorrhage, Dyer and co-workers routinely labeled erythrocytes with chromium 51 in very sick newborns within the first few hours of life. In those infants with IVH who died, chromium 51 was always present in the intraventricular clot; this clearly indicated that hemorrhages were postnatal events. Using the same technique, Tsiantos et al. found that 60% of the hemorrhages took place between 15 and 48 hours of age, with a mean age of 38 hours. Levene et al. using real-time ultrasound, showed that most hemorrhages occurred during the first two days of life. However, they observed that 25% occurred as late as 10 days of age. W. performed the first ultrasound as soon as possible after delivery (ie, within six hours); in four newborns, the first ultrasound showed hemorrhage. In three cases, there was SEH only. No new hemorrhage was detected in any infant after 72 hours of age. Therefore, we are not able to exclude events at the time of labor and delivery from having etiologic significance in the occurrence of IVH.

A positive correlation between the time of the IVH and the gestational age of the infant, has been reported. Using adult hemoglobin as a marker, observed that infants less than 28 weeks' gestation were more likely to sustain SEH/IVH in the first 24 hours of life than infants of greater gestational age in whom hemorrhages occurred between 12 to 72 hours. The authors concluded that the earlier hemorrhages in infants whose gestational ages were less than 28 weeks were probably related to adverse perinatal factors, whereas postnatal factors were the prevalent cause of hemorrhage in infants of greater gestational age. Although we did not show such absolute division of timing in relation to gestational age, we agree that perinatal factors are important with regard to etiology in those babies of less than 29 weeks' gestation who sustain IVH/SEH. Furthermore, we speculate that our aggressive approach may play a role in prevention of IVH/SEH in infants whose gestational age is greater than 29 weeks.

It is important to delineate clearly the population at highest risk of developing SEH/IVH. From our study, it would appear that in the setting of a perinatal unit, only newborn infants of 29 weeks' gestational age or less are at risk, and it is to this group that preventive measures should be applied.

Hambleton and Wigglesworth have clearly shown that SEH/IVH originates in the subependymal layer, probably, they feel, as a result of capillary rupture, caused by an increase in blood pressure when these capillaries are already maximally dilated secondary to hypercapnia and hypoxia. A positive correlation has been found between the incidence of SEH/IVH and the use of intermittent positive pressure ventilation (IPPV), occurrence of metabolic acidosis, hypercapnia, and hypoxia and the use of alkali infusions. We believe that the early institution of ventilatory support minimizes the etiologic influences of hypercapnia and hypoxia, and no infants in the study received infusions of alkali during resuscitation. We found no correlation between cord blood POCO2 and the subsequent occurrence of SEH/IVH as has been described elsewhere.

There is controversy in the literature about the association of pneumothorax and SEH/IVH. The above results suggest that pneumothorax is not a factor in the etiology of SEH/IVH. However, the sample size is small and further
research is necessary to establish the stability of this finding.

ACKNOWLEDGMENTS

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