Risk factors in the development of intraventricular haemorrhage in the preterm neonate

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SUMMARY One hundred and forty-six infants of 34 weeks’ gestation or less were repeatedly scanned by means of real-time ultrasound to diagnose the presence of intraventricular haemorrhage (IVH), its severity, and the timing of onset of the condition. We describe a new method for grading the extent of the IVH which does not depend on ventricular size. IVH was clearly present in 52 (36%) of the 146 infants and in 32 (50%) of the 64 infants of 30 weeks’ gestation or less. Repeated scans accurately timed the onset of IVH in 41 infants, and 32 (78%) had the first sign of IVH before 72 hours of age. Thirty-two clinical factors were analysed for possible correlation with the development of IVH: outborn compared with inborn, administration of sodium bicarbonate, hypothermia, intermittent positive pressure ventilation, continuous positive airways pressure, hypercapnia, severe acidosis, and respiratory distress syndrome all reached statistical significance. Analysis of variance showed that respiratory distress syndrome was the most important factor, but severe acidosis had some independent action on the development of IVH. Seventeen (81%) of 21 infants with hypercapnia (PCO₂ > 6 kPa) together with severe acidosis (pH < 7.1) developed IVH, of which more than half was moderate or severe in degree.

Real-time ultrasound is a safe and non-invasive method of diagnosing intraventricular haemorrhage (IVH) with a high degree of accuracy.1–5 At-risk infants can repeatedly be examined to time the onset and severity of the haemorrhage. Knowledge of timing allows analysis of clinical events predating the onset of the IVH; these may then be analysed statistically to determine their importance in the causation of the condition. This paper describes such a study.

Methods

From the beginning of November 1979 until the end of February 1981, unselected admissions to the neonatal intensive care unit at Hammersmith Hospital were prospectively and regularly examined with real-time ultrasound. Infants were included in the study group if they survived long enough to have at least one ultrasound examination of the head. The first examination was performed within 36 hours of admission to the neonatal unit by the method previously reported.6 All scans were performed using a Kranzbühler ADR linear array machine fitted with a 5 or 7 MHz transducer.

Gestational age was determined from maternal dates and gestational assessment by the method of Dubowitz et al.6 If maternal dates were uncertain or if there was a discrepancy of more than 2 weeks an assessment of maturity was taken as the true gestational age. All infants were weighed on admission and their birthweight for gestation calculated from charts. Infants were considered to be small for gestational age if their birthweight was below the 10th centile for gestational age on the charts of Gairdner and Pearson,7 or to be very small for gestational age if their birthweight fell below the 3rd centile of Usher and McLean.8

The infants were studied irrespective of their place of birth. Some were local babies born at Hammersmith Hospital, others were transferred in utero from other hospitals to be delivered at Hammersmith, and a third group was born outside the hospital and transferred in. Infants in the last group were transferred at varying postnatal ages, but were not included in the study unless they were 72 hours of age or less on admission. In addition, if IVH was diagnosed by ultrasound on arrival at Hammersmith Hospital they were not included, as events predating the haemorrhage could not be accurately determined.

Infants were initially scanned daily if possible for at least the first week of life; thereafter they were
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methods
the IVH.
Grading
recorded.
arteriosus
was
was
murmur
of
blood cultures
7.

Hypercapnia was considered to be mild if an arterial blood gas recording exceeded 6 kPa, and to be severe if it exceeded 8 kPa. Acidosis was considered to be of moderate degree if an arterial pH was estimated at between 7.1 and 7.2, and severe if any pH below 7.1 was recorded. Infection was assigned as present if positive blood cultures were obtained, or a strong clinical suspicion of infection was present. A patent ductus arteriosus was considered present if a characteristic murmur was heard together with a collapsing pulse.

Grading the IVH. Grading the size of the IVH has caused considerable confusion as there are several methods in use all of which use the size of the lateral ventricles.2 9-13 Flodmark et al.18 have questioned the validity of such grading systems. They studied the relationship between the ventricular size, the degree of IVH, and postnatal age. Infants examined after 2 days not only had larger ventricles but showed increasingly severe enlargement for each progressive grade of IVH. This indicates that after age 2 days the ventricular size is as much related to the postnatal age as to the extent of the haemorrhage. For these reasons they felt that neither the amount of ventricular blood nor the size of the ventricles was a good index to use for grading the extent of IVH.

Liquid blood in the ventricles will probably not be detected by ultrasound, and any grading system...
based on liquid blood (like all computerised tomography (CT) studies) is unlikely to be of particular value. In the light of Flodmark and colleagues’ remarks our grading system is dependent on the size and extent of the cerebral haemorrhage, and not on the ventricular component. In this study we have graded germinal matrix or intraventricular haemorrhages into mild, moderate, and large, and described the ventricular size separately.\(^{14,15}\)

**Grade 1.** Mild haemorrhage, originating in the region of the germinal matrix with no inferior or lateral extension beyond the most lateral border of the lateral ventricle.

**Grade 2.** Moderate haemorrhage with some downwards extension into the basal nuclei on at least one side, or involvement of the caudate nucleus to the region of the genu of the lateral ventricle posteriorly on parasagittal scans.

**Grade 3.** Large haemorrhage, with any degree of extension laterally or superiorly into the cerebral parenchyma.

These three grades are shown in Fig. 1.

**Statistics.** Two different methods of statistical analysis were performed. Initially in an attempt to select clinical items which may have had an important bearing on the development of IVH a series of \(2 \times 2\) \(\chi^2\) analyses with a Yates’s correction was done. Where appropriate Fisher’s exact test was used instead of, or as well as, the \(\chi^2\) analysis. The factors that correlated strongly with IVH on the above analyses were then re-examined to determine whether they acted independently of each other. This was done by multiple regression analysis adapted to discrete data (generalised linear interactive modelling—"GLIM"\(^{16}\)).

**Results**

One hundred and forty-six infants were studied. Their gestational ages ranged from 27 to 34 (median 31) weeks and their weight from 705 to 2920 (median 1390) g. The number of scans each infant received ranged from 1 to 41. Thirty (21\%) of the infants were born at Hammersmith Hospital to mothers living locally. Fifty-nine (40\%) were in utero transfers born at this hospital, and 50 (34\%) were born outside and transferred here.

Overall, 52 (36\%) of the 146 had IVH and in 7 (5\%) infants no clear diagnosis could be made; these infants were designated as having equivocal scans. The degree of severity of the haemorrhage was graded as described earlier and Table 2 shows the distribution of haemorrhage by gestational age group.

<table>
<thead>
<tr>
<th>Week</th>
<th>None</th>
<th>Mild</th>
<th>Moderate</th>
<th>Severe</th>
<th>Equivocal</th>
</tr>
</thead>
<tbody>
<tr>
<td>28-30</td>
<td>29</td>
<td>17</td>
<td>6</td>
<td>9</td>
<td>3</td>
</tr>
<tr>
<td>31-32</td>
<td>34</td>
<td>5</td>
<td>3</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>33-34</td>
<td>24</td>
<td>8</td>
<td>2</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>87</strong></td>
<td><strong>30</strong></td>
<td>11</td>
<td>11</td>
<td>7</td>
</tr>
</tbody>
</table>

The incidence of IVH of any grade of severity was broken down according to gestational age (Fig. 2) and there is a pronounced decline in frequency of IVH after 30 weeks’ gestation. Thirty-two (50\%) of 64 infants born at 30 weeks’ gestational age or less had IVH, whereas only 19 (23\%) of 81 born between 31 and 34 weeks’ gestational age had IVH (\(\chi^2 = 9.2, P = 0.02\)). Eleven (31\%) of the 36 infants of 33 and 34 weeks’ maturity had IVH compared with only 8 (18\%) of 45 of those born at 31 or 32 weeks’ maturity. The distribution of equivocal scans by gestational age is also shown in Fig. 2.

**Timing of the haemorrhage.** In 41 (79\%) of the 52 infants with IVH, frequent scanning permitted accurate timing of the haemorrhage to the nearest day (Fig. 3). Ten (24\%) of the 41 timed haemorrhages occurred within the first 24 hours of life, and
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32 (78%) of the 41 within 72 hours of birth. Only one infant (a boy born at 29 weeks) had a haemorrhage after the first week of life, and this was timed as occurring on day 11.

**Analysis of risk factors.** There were 83 boys and 63 girls in the study of whom 29 (35%) and 23 (37%) respectively developed IVH. Twenty-two (15%) infants died, 11 of whom were boys, and 12 (55%) of these 22 infants had IVH (9 boys and 3 girls).

In the most immature group (30 weeks and below) the incidence of IVH ranged from 49% for the in utero transfers to about 60% for the locally delivered babies and postnatal transfers. In the more mature groups, outborn babies had a higher incidence of IVH than either the local babies or the in utero transfers born at Hammersmith Hospital.

All the risk factors were compared against the presence or absence of IVH irrespective of grading. Table 3 shows factors that reached statistical significance. Of the obstetric factors, only place of birth was important when in utero transfers were compared with outborn infants (P = 0.03). Of the neonatal factors sodium bicarbonate administration to the infant, infection, and hypothermia all reached at least the 5% level of significance. Twenty-three infants received base, all by slow intravenous infusion and 14 developed IVH. The median volume of THAM was 1.9 ml/kg in infants without IVH, and 2.6 ml/kg in those with haemorrhage. The median amount of sodium bicarbonate was 1.70 mmol/kg in those without IVH, and 1.55 mmol/kg in those with it. Comparisons of amounts given to infants with and without IVH showed no significant difference using the Mann–Whitney U test.

Respiratory complications in the infants were most highly correlated with haemorrhage. Respiratory distress syndrome (RDS) (P < 0.0001), and the requirement for respiratory support either by intermittent positive pressure ventilation (IPPV) (P < 0.001), or continuous positive airways pressure (CPAP) (P < 0.001), were all highly associated with the presence of IVH. Any degree of hypercapnia (P < 0.001) had a strong association with haemorrhage and acidosis with a pH of below 7.1 being strongly related to IVH (P < 0.001). Mild acidosis (pH 7.1 to 7.2) showed no difference when compared with non-acidotic infants (P = 0.30). Twenty-one infants had some degree of hypercapnia as well as severe acidosis, and 17 (81%) developed IVH, 9 of whom had moderate or severe degrees of haemorrhage.

**Analysis of variance.** The following factors which correlated strongly with IVH on χ² analyses were considered together: RDS, IPPV, hypercapnia, severe acidosis, the administration of base, and gestational age. Analysis of scaled deviance by means of 'GLIM' showed that the best predictors of IVH were RDS and severe acidosis, with IPPV and gestational age having a lesser effect. In an initial analysis the administration of base showed low predictive value; therefore in the second analysis gestational age was substituted for it. The influence of hypercapnia and infusions of base appeared to be negligible once the other factors had been allowed for. The prediction equation was: Logit (P) = 0.99 RDS + 0.62 IPPV + 0.48 hypercap + 0.91 acidosis + 0.69 gestational age where P is the probability of IVH. RDS, severe acidosis, and IPPV were given the value of 1 if present and 0 if absent, and gestational age the value of 1 if < 30 weeks, or 0 if > 31 weeks.

![Diagram](image_url)

**Fig. 3** Timing of intraventricular haemorrhage in days. Last column (U) represents those infants in whom accurate timing was not possible.

**Table 3 Factors that reached statistical significance on χ² analysis**

<table>
<thead>
<tr>
<th></th>
<th>IVH</th>
<th>No IVH</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>In utero transfer</td>
<td>17/58</td>
<td>35/81</td>
<td>0.03</td>
</tr>
<tr>
<td>Bicarbonate infusion compared with no base</td>
<td>9/12</td>
<td>3/74</td>
<td>0.02</td>
</tr>
<tr>
<td>Respiratory distress syndrome</td>
<td>36/61</td>
<td>16/78</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>IPPV</td>
<td>31/49</td>
<td>21/90</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CPAP</td>
<td>24/37</td>
<td>27/99</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Mild hypercapnia</td>
<td>13/25</td>
<td>38/111</td>
<td>0.003 (0.004)</td>
</tr>
<tr>
<td>Severe hypercapnia</td>
<td>24/37</td>
<td>27/99</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Severe acidosis</td>
<td>17/21</td>
<td>34/115</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hypothermia</td>
<td>12/20</td>
<td>40/119</td>
<td>0.045 (0.048)</td>
</tr>
</tbody>
</table>

Figures in brackets represent significance for Fisher’s exact test.
Grading the IVH. Thirty infants had mild IVH, 11 moderate, and 11 severe. Fig. 4 shows the grade of IVH expressed as a percentage by gestational age group. The less mature the infant the greater is the proportion of severe haemorrhages that occur. When moderate and severe haemorrhages are considered together and compared with mild haemorrhages for two gestational age groups (30 weeks and below, and greater than 30 weeks) no statistically significant difference was found (Fisher’s exact test $P = 0.56$).

In order to further study the factors that influence the severity of the haemorrhage, mild IVH was compared with both moderate and severe haemorrhage grouped together. Multiple $\chi^2$ and Fisher’s analyses were performed as above. No neonatal factors at all showed any statistically significant difference at a 5% level, but fetal distress did reach statistical significance ($P = 0.049$).

Pathological correlation. CT was not available at Hammersmith Hospital during the 18-month course of this study. During this time 42 infants died who had been previously scanned, and of these 31 were submitted to necropsy. Table 4 gives details of these infants.

No clear diagnosis (equivocal scans) could be made in 2 infants, and neither had IVH at necropsy. Of the 29 in whom a diagnosis could be made, 18 were thought on ultrasound to have IVH, and this was confirmed at necropsy in 15. No false-negative diagnoses were made. The overall agreement be-

tween definite ultrasound diagnosis and necropsy findings was 26 (90%) out of 29.

Discussion

This study has confirmed that cerebral real-time ultrasound diagnosis agrees with necropsy findings in 90% of infants for presence or absence of haemorrhage. This compares favourably with the accuracy of CT in the detection of this condition.

We have also shown that certain identifiable risk factors make the development of IVH in the preterm infant much more likely. RDS, mechanical ventilation, hypercapnia, acidos, infusion of base, and gestational age all correlate highly with the onset on IVH. Analysis of variance has shown that many of the factors are interdependent, and mechanical ventilation and hypercapnia probably reflect the severity of the RDS. Acidosis exhibits some independent action but the infusion of base is related to the acidoses, and is not very important in its own right.

The finding that RDS and consequent hypercapnia are important risk factors is not new. Hypercapnia was initially suggested as being important in the development of IVH in 1961, and this condition has been subsequently found to correlate highly with IVH by a number of investigators, although Kosmetatos et al. could not confirm it.

Historically the analysis of neonatal risk factors for the development of IVH has relied on necropsy data with all its attendant limitations. More recently with the advent of CT scanning the incidence of the condition has been studied in living infants. Frequent re-examinations of the babies have not been possible and timing of the event was not attempted. Without this knowledge consideration of risk factors could not be positively allocated to cause or effect of the haemorrhage. Ultrasound does permit repeated re-examination with no risk to the infant, and we have attempted to analyse the risk factors in infants with IVH only up to the time of the haemorrhage. In those without IVH the risk factors were analysed up to the end of the first week of life as only one of the 41 infants developed a cerebral haemorrhage later.
The relationship between maturity of the infant and development of haemorrhage showed a high incidence of IVH in the least mature infants and this is well known. Half the infants of 30 weeks or less had IVH in this study. There was however a striking decrease in the incidence of haemorrhage after the 30th postmenstrual week, and this is perhaps of importance in consideration of the timing of delivery in a compromised fetus. The reason for the fall in prevalence of IVH at this time is probably related to maturation of the vascular anatomy or to the physiology of cerebral autoregulation affecting the germinal matrix capillaries.

The age at onset of IVH has until recently been inferred from necropsy material, and is likely to reflect a bias towards more severe and therefore lethal haemorrhages. Although IVH has been reported in the stillborn infant, it is generally a condition that occurs after birth. Various methods designed to time the onset of haemorrhage have depended on analysis of the proportion of radioactively labelled red cells or the proportion of adult erythrocytes in the intracerebral clot found at necropsy. The range for the onset of bleeding in 10 infants was between 3 and 96 hours in one study, although the median time appeared to be within the first 24 hours. Tsiantos et al. studied 78 infants, and 12 (16%) developed IVH before age 24 hours, half of them within 7 hours of delivery. These studies are of great interest but may only reflect timing of the most severe and fatal bleeds.

Despite a number of studies of IVH in living infants using either CT or ultrasound to diagnose the IVH there have been no reports on precise timing of the onset of haemorrhage. This study shows that of 41 infants in whom accurate timing was possible, nearly 80% developed the lesion within 72 hours of birth, and late haemorrhage was rare. This agrees well with the work of Tsiantos and colleagues.

More haemorrhages occurred in infants who were born outside the hospital and then transferred here than in infants born here, and this reached statistical significance when in utero transfers were compared with outborn babies. This difference disappeared when the maturity of the infants was further broken down owing to smaller numbers. The in utero transfers consistently had the lowest incidence of IVH irrespective of maturity but it is difficult to draw conclusions from these data because the babies did not represent a population study. Generally in utero transfers had a lower incidence of haemorrhage, probably because they were considered to be a high-risk group with consequent close monitoring and special attention.

Few studies have considered the place of birth and related it to IVH. Dykes et al. could find no significant difference in the incidence of IVH between inborn and outborn infants, but they did not appear to admit to hospital all babies below a given birthweight or gestational age, and therefore place of birth must be considered to be as yet an unproved risk factor. It is probable that during transport cardiorespiratory complications are likely to arise and be undetected which would probably predispose the infant to haemorrhage.

Disregarding place of birth, obstetric factors did not appear to influence the risk of IVH. In a review of data on necropsies an association between IVH and maternal infection, pre-eclamptic toxemia and primiparity was found but this was not confirmed by studies of IVH diagnosed in life.

Conflicting reports have appeared on the risk of IVH in growth-retarded infants. This study did not find that intrauterine growth retardation predisposed to haemorrhage whether the growth failure had been mild or severe. Multiple gestation has also been implicated in predisposing to IVH but this has not been found by other investigators, nor was it so in this study.

Cardiorespiratory complications of neonatal care have long been considered to be the most important predisposing risk factors in the development of IVH. RDS as discussed above, and its treatment by CPAP or IPPV are such factors. In this study RDS, CPAP, and IPPV all correlated very strongly with the development of IVH. In the Hammersmith Hospital neonatal unit few of the most immature infants received CPAP without IPPV, although in the subgroup of 31 to 34 weeks CPAP alone was thought to be justified for moderate to severe RDS. Consequently the strong association between CPAP and IVH in the least mature subgroup probably reflected the hazards of IPPV as this was the principal form of treatment.

Severe acidosis was found to be an important and independent factor in the development of IVH, although mild acidosis (pH 7.1 to 7.2) did not appear to increase the risk of haemorrhage. Again there is conflicting evidence from two previously reported studies in living infants on whether acidosis is an important risk factor in the development of IVH. Kosmetatos et al. stated that it was, whereas Dykes et al. did not find it was so. The acidosis may reflect poor tissue perfusion and in fact be secondary to hypotension but as it was not possible to measure blood pressure continuously in all the infants in this study, this must remain speculative.

Wigglesworth et al. noted that in infants above 30 weeks' gestation IVH virtually did not occur without RDS and suggested that this might be due to the management of the condition.
al. also suggested that the administration of base might be associated with intracranial haemorrhage. Whether or not the base had been given before or after the onset of haemorrhage has been much debated, but prospective studies have suggested that rapid infusion of hyperosmolar sodium bicarbonate was associated with a significantly increased incidence of IVH and Dykes et al. found that the administration of sodium bicarbonate after the first day of life was also a significant risk factor. This present study found that significantly more base had been given to infants before the onset of the haemorrhage but this was secondary to severe acidosis for which the base was given. The volumes of base used in this study are small, and have been infused slowly. It is possible that if massive amounts were again to be given, as in previous years, this factor might actually produce IVH by its hyperosmolar effect.

The cumulative effect of RDS and severe acidosis appeared to give a good prediction of which babies would develop IVH. Seventeen (81%) of 21 infants with hypercapnia (an index of the severity of RDS) as well as severe acidosis developed IVH, 9 of whom had moderate or severe degrees of haemorrhage. Most authors agree that the greater the extent of the haemorrhage the more likely is there to be residual neurological handicap. It is possible that careful monitoring to detect and prevent mild degrees of hypercapnia, as well as correction of acidosis before the pH falls below 7.1 may reduce the incidence of more severe IVH, and consequently lessen the risk of long-term neurological handicap.

Hypothermia was found to be weakly associated with IVH, and does not seem to have been reported in previous prospective studies. Apnoea has been suggested as being of importance in the development of haemorrhage but was not found to be so in this study. In a previous paper we did not find it to be associated with IVH after haemorrhage had occurred. Changes in blood pressure could not be analysed as blood pressure was not regularly measured on infants during the main part of this study. The number of transfusions, which may reflect episodes of hypotension, did not however correlate with IVH.

It is clear from Fig. 4 that the more immature infants tend to have more severe haemorrhages and consequently fewer mild ones. This trend reverses with maturity up to 34 weeks, but the severity of risk factors does not seem to influence the eventual size of the haemorrhage. Another factor that may influence the maximum extent of the haemorrhage is the anatomical position of the initial lesion. Pape and Wigglesworth describe massive venous infarction after germinal matrix haemorrhage due to obstruction of the terminal veins, and it is conceivable that secondary venous infarction may occur after a fairly small haemorrhage if it was in close proximity to these vessels. This would give the appearance of extensive haemorrhage and is probably indistinguishable on ultrasound from true intraparenchymal haemorrhage resulting from extension of a germinal matrix bleed.

From this study and from those of others it is apparent that there is no single predisposing cause of IVH, but that multiple factors may be important to a lesser or greater degree depending on the maturity of the infant. It is clear that in order to minimise the risk of IVH in preterm infants observational attention must be paid to their management. Continuous monitoring of carbon dioxide tension when readily available will be vital, and close attention to blood pressure and pH may also be of great importance in an effort to avoid major fluctuations. With this attention to detail in the management of the at-risk infant, IVH may be avoided and the chance of subsequent handicap be reduced.

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