Archives of Disease in Childhood, 1984, **59**, 631–636

Extension of neonatal intraventricular haemorrhage

M I LEVENE AND L DE VRIES

Department of Paediatrics and Neonatal Medicine, Royal Postgraduate Medical School, Hammersmith Hospital, London

SUMMARY A total of 338 infants of gestational age 34 weeks or less were scanned regularly with real time ultrasound. Definite intraventricular haemorrhage was present in 126 (37%) infants, of whom 17 (13·5%) showed extension in the size of the initial haemorrhage, mostly into the cerebral parenchyma. These 17 infants were carefully matched with 17 others who had an initial haemorrhage of the same size and the same number of adverse perinatal factors. On analysis those infants with extension of intraventricular haemorrhage were constantly more acidotic and more anaemic than the control group. It is possible that careful attention to maintaining optimal condition after the onset of intraventricular haemorrhage may reduce the risk of extension.

With the introduction of computed tomography in infants of very low birthweight and the subsequent widespread use of real time ultrasound scanning of the neonatal brain, our understanding of intracranial haemorrhage in preterm infants has expanded considerably and follow up data is now becoming available on the long term effects of intraventricular haemorrhage. A number of workers have shown that handicap is related to the size of the haemorrhage[1 2] and others have attempted to reduce its incidence by drug treatment.[3 4] In 1981 Donn and Stuck[5] reported five infants in whom documented intraventricular haemorrhage subsequently extended to the cerebral parenchyma. We had noted similar findings and considered whether infants suffering extension of haemorrhage differed from those without extension—the implication being that preventable factors may operate that predispose the infant to intracerebral extension which is also likely to be associated with a greater risk of handicap. To identify possible risk factors we studied 17 infants who had documented evidence of extension in the size of their initial haemorrhage.

Patients and methods

All infants admitted to the neonatal intensive care unit of this hospital between February 1980 and May 1982 of gestational age 34 weeks and below who had had at least two ultrasound scans performed were included in the study. For the first 10 months of the study scans were performed on an ADR linear array machine with a 7 MHz transducer and for the remaining 18 months an ATL mechanical sector scanner with a 5 MHz transducer was used.

The infants were scanned frequently and those who developed intraventricular haemorrhages which had increased in size on subsequent scans were selected to be the 'intraventricular haemorrhage extension' group (Figs. 1 and 2). The medical records of these infants were carefully inspected to document the severity of their perinatal illness, and the number of adverse factors (maximum 8) was noted for each infant. These adverse factors comprised: outborn delivery, birth asphyxia (Apgar score of 5 or less at 5 minutes or the requirement for intubation lasting more than four minutes, or both), intermittent positive pressure ventilation for more than 24 hours, pneumothorax, hypoglycaemia, necrotizing enterocolitis, proved septicaemia, and a patent ductus arteriosus requiring treatment. Each of the infants with extension of intraventricular haemorrhage was carefully matched with a control infant of the same gestational age, who had suffered the same number of adverse perinatal factors, and whose intraventricular haemorrhage was the same size as that of the index baby when first noted on ultrasound scan. The three point grading system used to describe the severity of haemorrhage has been previously reported.[6]

The infants' medical records were examined again to extract details of blood gases, packed cell volume, and clinical events occurring between the time of the initial intraventricular haemorrhage and the time

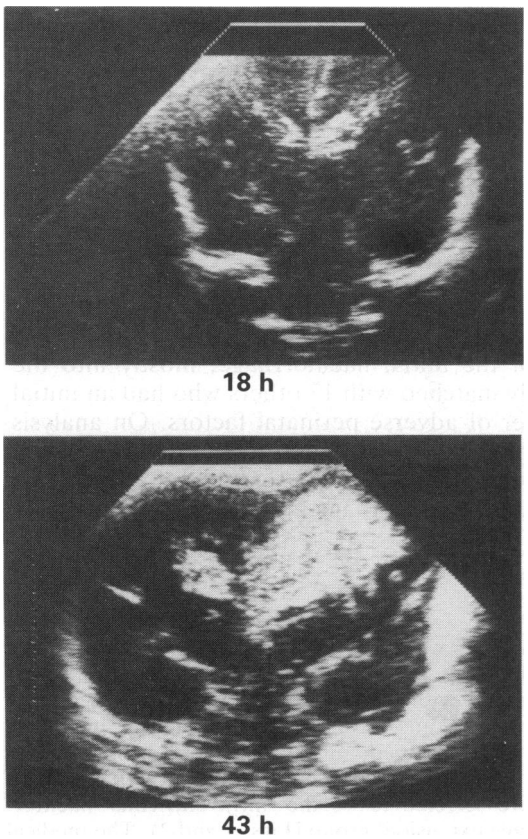

Fig. 1 *Two coronal ultrasound scans at 18 and 43 hours in an infant of 28 weeks' gestation weighing 1080 g. The scan at 18 hrs shows a small grade II haemorrhage on the right side which has extended into a massive parenchymal haemorrhage at 43 hours. There is thrombus in the left lateral ventricle on the scan at 43 hrs.*

the haemorrhage reached maximum size or, in the control group, until three days had elapsed from the first ultrasound diagnosis of intraventricular haemorrhage (the 'interextension period'). Tables 1 and 2 list the details elicited from the babies' charts. All blood gas estimates made during the interextension period in both groups were recorded and the proportion of abnormal results was tabulated. Table 1 gives the definitions used to determine whether any one blood gas value was abnormal. In addition, the period of time the infants remained acidotic was estimated by calculating the number of hours the arterial pH remained less than 7·2. The median pH and packed cell volume values were plotted graphically with time (Figs. 3 and 4). Statistical analysis compared the weighted proportions of abnormal gases for each infant pair using a logistic model and GLIM computation.[7] Final analysis was performed by a paired Student's *t* test or Wilcoxon rank sum test.

Results

During the 28 month period, 338 infants fulfilled the criteria for admission to the study. A total of 126 (37%) had intraventricular haemorrhages and 19 infants (6%) had equivocal scans. In the latter group no definite ultrasound diagnosis could be made. Sixty four (19%) of the 338 infants died and 40 (32%) of the 126 with intraventricular haemorrhages died. Mortality in infants without haemorrhage was 18 of 193 (9%). The mortality and proportion with bilateral haemorrhage related to the size of haemorrhage is shown in Table 3. Forty (32%) of the infants had bilateral intraventricular haemorrhages.

The size of the initial bleed extended in 17 (13·5%) of the 126 infants with intraventricular haemorrhages

Table 1 *Number of infants with abnormal blood gases and total number of abnormal blood gas estimates in the 17 infants with extension of intraventricular haemorrhage (IVH) and the 17 control infants*

	No of infants with abnormal blood gases (n=17)		*No of abnormal blood gases*		*Statistical significance*
	IVH extension group	*Control group*	*IVH extension group*	*Control group*	
Hypoxia (Pao_2 <6 kPa)	7	6	10	14	NS
Hyperoxia (Pao_2 >12 kPa)	6	8	9	14	NS
Hypercapnoea ($Paco_2$ >6 kPa)	11	15	43	72	NS
Severe hypercapnoea ($Paco_2$ >8 kPa)	6	6	21	21	NS
Acidosis (pH <7·2)	13	7	40	18	P<0·01
Severe acidosis (pH ≤7·1)	8	4	17	8	P<0·01
Metabolic acidosis (base deficit ≥10)	12	9	31	18	P=0·05
Total number of blood gas estimates			152	215	

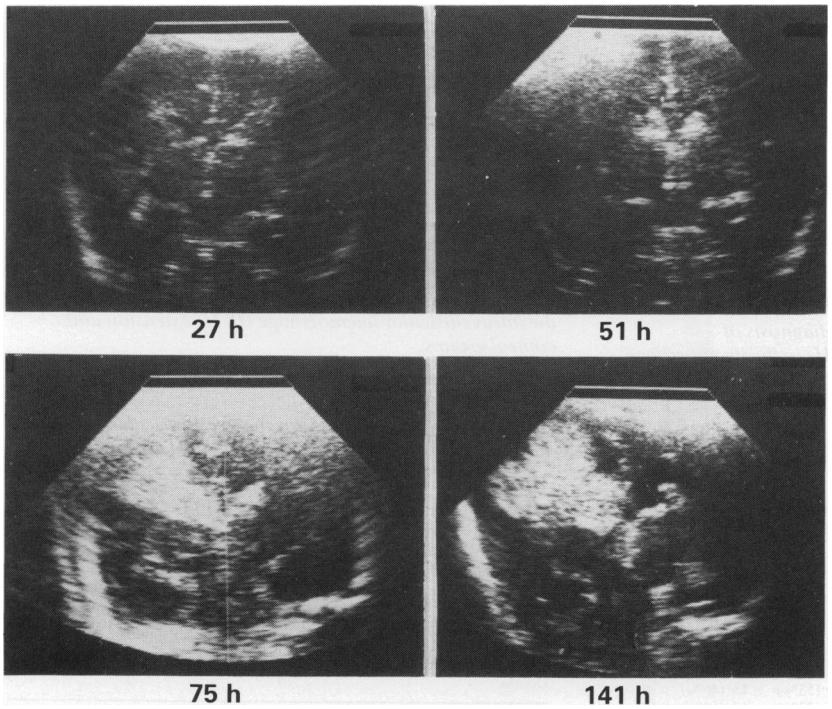

Fig. 2 *Serial coronal scans of a girl of 29 weeks' gestation weighing 1120 g at birth. The initial scan shows a very small grade I haemorrhage on the right. Subsequently bilateral haemorrhages occurred (51 hours) and the lesion on the left extended into a massive intraparenchymal haemorrhage by 141 hours. There is some dilatation of the right lateral ventricle on the final scan.*

Table 2 *Details of abnormal results of investigations, treatments, and drugs given to the 17 infants with extension of intraventricular haemorrhage (IVH) and 17 control infants*

	No of infants		*No of episodes*	
	IVH extension group	*Control group*	*IVH extension group*	*Control group*
Transfusions (plasma or blood)	7	3	9	6
Hypernatraemia (sodium >150 mmol/l	5	3	7	5
Polycythaemia (packed cell volume >0·65)	0	1	0	1
Pneumothorax	4	2	4	2
Hypotension (systolic blood pressure <30 mm Hg)	4	1	4	1
Buffer (bicarbonate or THAM)	2	2	4	5
Tolazoline	1	1	1	1
Aminophylline	2	1	2	1
Frusemide	3	1	3	1

THAM=trihydroxymethylaminomethane.

from grade I to grade II in five infants, from grade I to grade III in 6, from grade II to grade III in four, and from a small intraparenchymal intraventricular haemorrhage (grade III) to a massive parenchymal haemorrhage (grade III+) in two infants. There were no differences between the infants in the haemorrhage extension and control groups (Table 4) and infants in both groups had a similar number of ultrasound scans in the first week of life. There were 10 deaths in the intraventricular haemorrhage extension group and 9 in the control group. Infants first developed haemorrhage at a median age of 35 (range 3 to 62) hours in the intraventricular haemorrhage extension group and 48 (range 1 to 123) hours in the control group. All infants who extended their haemorrhages did so within three days of the initial haemorrhage. The ages at which the diagnosis of intraventricular haemorrhage was first made and the haemorrhage reached its maximal extent are shown in Table 5: the number of scans performed between the initial detection and the maximal extent of the haemorrhage is also shown in this table. Extension

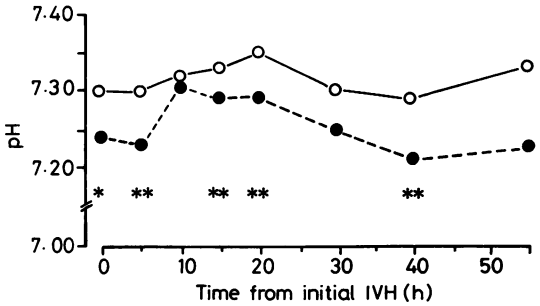

Fig. 3 *pH values after the initial diagnosis of intraventricular haemorrhage (IVH) in the haemorrhage extension (closed circles) and control (open circles) groups. (*Represents P<0·05, **represents P<0·01).*

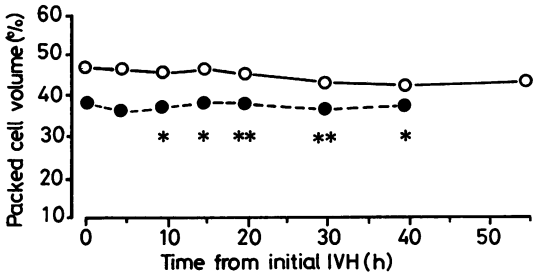

Fig. 4 *Packed cell volume after the initial diagnosis in the intraventricular haemorrhage (IVH) extension and control groups.*

Table 3 *Proportion of bilateral intraventricular haemorrhages (IVH) and mortality related to grade of IVH*

	Grade of IVH			*Total*
	I	*II*	*III*	
All infants with IVH	68 (54%)	30 (24%)	28 (22%)	126
Infants with bilateral IVH	11 (16%)	16 (53%)	13 (46%)	40
Deaths	13 (19%)	10 (33%)	17 (61%)	40

Table 4 *Details of the infants in intraventricular haemorrhage (IVH) extension and control groups*

	IVH extension group (n=17)	*Control group (n=17)*
Gestational age (weeks). Median (range)	29 (27–32)	29 (26–34)
Birthweight (g). Median (range)	1080 (800–1500)	1090 (700–1980)
Boys	9	10
Small for gestational age*	4	4
Deaths	10	9

*Taken as below the 10th centile from the data of Gairdner and Pearson.[16]

Table 5 *Timing and frequency of ultrasound scanning in 17 infants who suffered extension of intraventricular haemorrhage (IVH)*

Infant No	*Age at diagnosis of IVH (hrs)*	*Age at maximal extension (hrs)*	*Interextension period (hrs)*	*No of scans in interextension period*
1	17	41	24	1
2	13½	37½	6	0
3	3	29	26	2
4	42	46	4	0
5	46½	118½	72	3
6	35	86	51	1
7	52½	78	25½	0
8	34	84	50	2
9	57½	83	25½	0
10	5	45	40	1
11	9	78½	68½	2
12	38	106	68	3
13	62	68	6	0
14	19	40½	21½	0
15	37½	64½	27	1
16	6	36	30	1
17	39	55	16	2

occurred at a median time of 26 hours after onset of the intraventricular haemorrhage.

Table 1 shows the number of blood gas estimates performed on infants in each group. Factors related to acidosis all seemed to be strongly associated with extension of haemorrhage (P<0·01). The total number of hours between the onset of haemorrhage and extension was 622 for the 17 infants with intraventricular haemorrhage extension and 1038 for the control group (that is, 72 hours from the onset of haemorrhage or time from haemorrhage until death). There was a highly significant differ-

ence in the duration of prolonged acidosis in the haemorrhage extension group compared with the control infants ($P<0.001$). A large base deficit indicated that the acidosis was metabolic in origin ($P=0.05$). Fig. 3 shows graphically the pH changes in the two groups. At initial diagnosis of intraventricular haemorrhage there was a difference in pH ($P<0.05$) and this remained consistent for the next 55 hours, after which there were few infants who had not yet extended their haemorrhage. Statistical analysis could not be performed after 40 hours. Between 10 and 40 hours after the diagnosis of intraventricular haemorrhage there seemed to be a progressive decline in the pH of infants whose haemorrhages extended. Fig. 4 shows the packed cell volume data plotted in a similar manner. Although the infants who extended their haemorrhages showed a consistently lower median packed cell volume for successive hours after the initial diagnosis, this did not reach statistical significance until 10 hours after haemorrhage ($P<0.05$). Insufficient packed cell volume data for further analysis was available in the haemorrhage extension group after 40 hours.

Clinical factors are shown in Table 2. There were more episodes of plasma and blood infusion, pneumothorax, and hypernatraemia in the haemorrhage extension group, although these differences were not pronounced. Blood pressure was not routinely measured during the course of this study and the periods of hypotension refer to clinically apparent 'shock' when the blood pressure was determined. The numbers are too small for statistical analysis. The number of infants to whom buffer (sodium bicarbonate or trihydroxymethylaminomethane) was given was similar in both groups.

Discussion

Factors correlated with the development of intraventricular haemorrhage include respiratory distress syndrome,[6 8 9] pneumothorax,[10] respiratory support, hypercapnea,[11] changes in blood pressure,[12] acidosis,[6] place of birth,[13] and use of hypertonic infusions.[9 14] Few studies have timed accurately the onset of haemorrhage in an attempt to elucidate predisposing factors. In one such report, however, respiratory distress syndrome and acidosis seemed to have individual and important action and over 80% of infants with both hypercapnea (an index of severity of respiratory disease) and severe acidosis developed intraventricular haemorrhages.[6] Hitherto, little attention has been paid to the period of vulnerability after the development of a small intraventricular haemorrhage, during which time extension, particularly into the cerebral parenchyma, may occur. Indeed, documentation of extension in the size of an intraventricular haemorrhage has only rarely been described. Donn and Stuck[5] reported five infants in whom extension of the initial haemorrhage was detected by real time ultrasound and Shankaran *et al*[15] described 6 infants with haemorrhage progression. This latter report, however, only seems to include infants whose ventricles dilated after the initial haemorrhage rather than true extension into the cerebral substance.

We found the incidence of extension of intraventricular haemorrhage in a large population of infants to be 13·5% and extension occurred within three days of the initial haemorrhage. Great care was taken to match infants in whom extension occurred with a control group who were equally ill. The 8 adverse perinatal factors were equally distributed between the two groups and the incidence of death was similar. During the course of the study those infants in whom haemorrhage was likely to extend could not be predicted and did not seem to have been scanned more frequently thereby anticipating their extension; both groups had the same number of scans within the first week of life. In addition, more blood gas measurements were performed in the control infants which, in the light of their severity of illness, was likely to weight this group to more abnormal results.

We have shown that infants in the haemorrhage extension group were considerably more anaemic and acidotic from the first diagnosis of intraventricular haemorrhage than the control group. Control infants did not become more anaemic after the haemorrhage, nor did their blood pH value drop. Conversely, the infants in the haemorrhage extension group became more acidotic approximately 30 hours after the initial diagnosis of intraventricular haemorrhage. The median timing of extension was 26 hours after the first ultrasound detection of haemorrhage and this was approximately the time that the major fall in the pH occurred. The more severe acidosis occurring at that time was probably related to the major extension.

It is apparent from this study that some infants developing intraventricular haemorrhage have remarkably normal packed cell volumes and are not acidotic. After the haemorrhage there is little change in these measurements and no further bleeding occurs. There is also a second group with intraventricular haemorrhage who are in worse condition (more anaemic and more acidotic) and in whom extension is more likely to occur. It is possible that transfusion and maintenance of blood volume with avoidance of metabolic acidosis may prevent the extension of a developed intraventricular

haemorrhage in this group. It follows that there may be important clinical indications for investigating infants at risk of intraventricular haemorrhage by regular, real time ultrasound scanning. In this way early intraventricular haemorrhages can be identified and, with careful attention to the maintenance of adequate perfusion and ventilation, further extension of haemorrhage may be avoided.

We thank Dr J S Wigglesworth, Professor V Dubowitz, and Dr A Whitelaw for help and encouragement; Professor Healey for advice with statistics and computing; Mrs A Cordwell for preparing the manuscript; and the Department of Medical Illustration, Royal Postgraduate Medical School for preparing the illustrations.

References

[1] Krishnamoorthy KS, Shannon DC, De Long GR, Todres ID, David KR. Neurological sequelae in the survivors of neonatal intraventricular hemorrhage. *Pediatrics* 1979;**64**:233–7.
[2] Thorburn RJ, Lipscomb AP, Stewart AL, Reynolds EOR, Hope PL, Pape KE. Prediction of death and major handicap in very preterm infants by brain ultrasound. *Lancet* 1981;**ii**: 1119–21.
[3] Donn SM, Roloff DW, Goldstein GW. Prevention of intraventricular hemorrhage in preterm infants by phenobarbitone: a controlled trial. *Lancet* 1981;**ii**:215–7.
[4] Morgan MEI, Benson JWT, Cooke RWI. Ethamsylate reduces the incidence of periventricular haemorrhage in very low birth weight babies. *Lancet* 1981;**ii**:830–1.
[5] Donn SM, Stuck KJ. Neonatal germinal matrix hemorrhage: evidence of a progressive lesion. *J Pediatr* 1981;**99**:459–61.
[6] Levene MI, Fawer C-L, Lamont RF. Risk factors in the development of intraventricular haemorrhage in the preterm neonate. *Arch Dis Child* 1982;**57**:410–7.
[7] Baker RJ, Welder JA. The GLIM system. Release 3. *Numerical algorithms*. Oxford: Release 3 1976:1–97.
[8] Harcke HT, Naeye RL, Storch A, Blanc WA. Perinatal cerebral intraventricular hemorrhage. *J Pediatr* 1972;**80**:37–42.
[9] Wigglesworth JS, Keith IH, Girling DJ, Slade SA. Hyaline membrane disease, alkali and intraventricular haemorrhage. *Arch Dis Child* 1976;**51**:755–62.
[10] Lipscomb AP, Thorburn RJ, Reynolds EOR, *et al.* Pneumothorax and cerebral haemorrhage in preterm infants. *Lancet* 1981;**i**:414–6.
[11] Cooke RWI. Factors associated with periventricular haemorrhage in very low birth weight infants. *Arch Dis Child* 1981;**56**:425–31.
[12] Lou HC, Lassen NA, Friis-Hansen B. Impaired autoregulation of cerebral blood flow in the distressed newborn infant. *J Pediatr* 1979;**94**:118–21.
[13] Clark CE, Clyman RI, Roth RS, Sniderman SH, Lane B, Ballard RA. Risk factors analysis of intraventricular hemorrhage in low birth weight infants. *J Pediatr* 1981;**99**:625–8.
[14] Papile LA, Burstein J, Burstein R, Koffler H, Koops B. Relationship of intravenous sodium bicarbonate infusions and cerebral intraventricular hemorrhage. *J Pediatr* 1978;**93**:834–6.
[15] Shankaran S, Slovis TL, Bedard MP, Poland RL. Sonographic classification of intracranial hemorrhage. A prognostic indicator of mortality, morbidity, and short term neurologic outcome. *J Pediatr* 1982;**100**:469–75.
[16] Gairdner D, Pearson J. A growth chart for premature and other infants. *Arch Dis Child* 1971;**46**:783–7.

Correspondence to Dr M I Levene, Department of Child Health, Leicester University Medical School, Leicester.

Received 1 March 1984