Periventricular-intraventricular haemorrhage in low-birth-weight infants at Baragwanath Hospital

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Abstract **The prevalence of periventricular-intraventricular haemorrhage (PV-IVH) among very-low-birth-weight infants at Baragwanath Hospital has not been well documented. In this prospective study, a total of 282 live-born infants with birth weights of 1 000 - 1 749 g were studied over a 4½-month period. Every infant had at least one cranial ultrasound examination at 7 - 10 days of age, while one-third of non-ventilated and all ventilated infants had ultrasound examinations on days 3, 7 and 14. Where possible, all infants had a follow-up ultrasound scan at 40 weeks' post-conceptional age. The overall prevalence of PV-IVH was 53% for infants weighing less than 1 500 g at birth and 52% for infants born at less than 35 weeks' gestation, but only 12% had either grade III or grade IV haemorrhages. The prevalence and severity of PV-IVH increased with both decreasing birth weight and decreasing gestational age and was also predicted by the need for active resuscitation at birth, mechanical ventilation and the development of pneumothorax. A total of 93% of infants without PV-IVH survived, but survival decreased with increasing grade of PV-IVH. Germinal matrix cysts were noted on follow-up in 55% of surviving infants with grade I PV-IVH. Very-low-birth-weight infants at Baragwanath Hospital therefore seem to have a higher prevalence of PV-IVH when compared with reported figures, but this is due mainly to an increase in smaller haemorrhages.**

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Periventricular-intraventricular haemorrhage (PV-IVH), defined as haemorrhage into the germinal matrix tissues with or without extension into the ventricular system and involvement of the cerebral parenchyma, remains a common problem in preterm infants.[1-3] This lesion is important not only because of its high prevalence and the serious nature of the larger haemorrhages, but also because major brain injury in premature infants occurs almost uniformly in the context of PV-IVH, either as an apparent consequence of the haemorrhage or as an associated finding.[1] The pathogenesis of PV-IVH is multifactorial, and different combinations of factors may be operative in different patients.[2] Not surprisingly, no single unifying cause of PV-IVH has been found.[3]

Over the last decade ultrasonographic transfontanelle sector scanning with a real-time machine has become accepted as the best technique for neonatal brain imaging. This has made the detection, staging and follow-up of PV-IVH reliable.[4-9] Cranial ultrasonography has become a routine screening procedure in very-low-birth-weight (VLBW) infants in most neonatal units. Variations in the prevalence of PV-IVH between institutions may be explained by differences in populations studied, varying definitions of abnormality, the timing and nature of ultrasound evaluations, and possibly different obstetric and neonatal practices in various centres. Low-birth-weight (LBW) infants at Baragwanath Hospital are known to have a high rate of intra-uterine growth retardation,[10] while many women delivering premature infants have not received proper antenatal care. Both these factors may modify the prevalence of PV-IVH. A previous study found a relatively high prevalence of PV-IVH at Baragwanath Hospital among a group of larger LBW infants,[11] but the prevalence of PV-IVH has not been systematically documented.

The purpose of this study was therefore to elucidate the prevalence, severity and short-term sequelae of PV-IVH in a defined group of LBW infants at Baragwanath Hospital and to compare these findings with those of other reported studies.

Methods

Baragwanath Hospital and the Soweto clinics provide a comprehensive perinatal service for the population of Soweto and surrounding areas and had over 20 000 in-hospital deliveries and approximately 12 000 clinic deliveries during 1989. Many infants born at home are brought to hospital after birth, and a small number of infants are transferred to the unit from outside hospitals, usually within the first 24 hours after birth. The neonatal unit has facilities to ventilate only 12 infants at a time and, owing to this limitation, the unit has had to adopt a policy of not ventilating infants weighing less than 1 000 g; all infants above this weight, however, are ventilated when clinically indicated. Since infants weighing less than 1 000 g at birth have a mortality of about 80%, many dying in the first 24 - 48 hours after birth, it was decided to exclude this group from the study as it was felt that it would not be practically possible to document PV-IVH for most of these infants. The upper weight limit for the study (1 749 g) was set because infants above this weight are not always admitted to the neonatal wards and selection bias would have been introduced if they had been included.

All infants with a birth weight between 1 000 and 1 749 g admitted to the neonatal unit at Baragwanath Hospital over a 4½-month period were eligible for this study. Infants with severe congenital abnormalities and those dying before a cranial ultrasound examination could be performed (this was most likely to occur after-hours) were recorded but excluded from subsequent analysis.

Gestational age was assessed clinically using the Ballard score[12] and infants were classified as small for gestational age (SGA) if they fell below the 10th percentile of Lubchenco's norms.[13] All relevant information relating to demographic factors, clinical details and laboratory investigations was documented prospectively for subsequent analysis of risk factors for PV-IVH in our population.

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Diagnosis of PV-IVH was made by transfontanelle real-time ultrasound examination, using a portable Kretztechnic Combison 310 sector scanner with a 7,5 MHz transducer. The cranial ultrasound technique used has been well described.[5,7-9] Ultrasound examinations were performed by three members of the neonatal division (K.D.B., R.Y.B., D.L.S.). During each ultrasound scan, coronal and parasagittal views were visualised and at least one image in each plane was recorded photographically. A final decision regarding the grade of PV-IVH for each infant was reached by consensus of all three sonographers. The most severe grade of PV-IVH recorded was used for each infant. To enable comparison with previous studies, Papile *et al.*'s[14] classification of PV-IVH was used as this still appears to be the grading system most widely employed, despite certain limitations.[15-17] In this classification, grade I constitutes germinal matrix bleeding only, grade II bleeding into one or both lateral ventricles, grade III sufficient bleeding into the lateral ventricles to cause acute ventricular dilatation, and grade IV associated intracerebral bleeding. Periventricular echodensities were recorded, but, since about 85% of these resolve without apparent sequelae,[15] only those resulting in cystic periventricular leucomalacia as described by Van de Bor *et al.*[18] were subsequently analysed in detail.

Every surviving infant had at least one ultrasound scan at 7 - 10 days of age. Owing to limitations of time and access to the ultrasound machine and the large number of infants studied over a relatively short period, it was not possible to do ultrasound scans earlier and more frequently on all infants. However, all infants who required mechanical ventilation and one-third of those who did not, allocated by random number generation, had ultrasound scans on at least 3 occasions at 3, 7 and 14 days of age. Ultrasound scans were done at any stage if clinically indicated and all infants with demonstrated PV-IVH were subsequently scanned every 7 - 14 days to detect the development of sequelae such as post-haemorrhagic ventricular dilatation and periventricular leucomalacia. Wherever possible, infants had a follow-up scan at 40 weeks' post-conceptual age. This was done either before hospital discharge or at the first neonatal follow-up appointment.

All data were entered onto a microcomputer and analysed using the Epi Info program.[19] Statistical analysis of data was performed using χ^2 analysis for discrete variables; when an expected cell was < 5, Fisher's exact test was used. When multiple intergroup comparisons were done, the usual significance level of 0,05 was adjusted using the Bonferroni correction. To assess risk factors for PV-IVH, a univariate analysis was initially performed using the grade of PV-IVH as the dependent variable. This was then analysed further using multiple linear regression analysis. The study was approved by the Committee for Research on Human Subjects of the University of the Witwatersrand.

Results

A total of 305 infants with birth weights of 1 000 - 1 749 g were enrolled over the period from the beginning of August to mid-December 1989. Fifteen infants died before a cranial ultrasound examination could be performed, 10 within 24 hours of birth. An additional 8 infants had major congenital abnormalities and all but 1 of these died. In terms of the study protocol, these 23 infants were excluded from further analysis. The study population therefore consisted of 282 infants. All the 68 infants who required mechanical ventilation within 48 hours of birth had their first ultrasound scan by the 3rd day of life with a minimum of 2 repeat scans at 1 and 2 weeks of age (unless they died earlier). According to the protocol, 79 of the 214 non-ventilated infants were randomly assigned to have ultrasound scans on days 3, 7 and 14, while a further 18 had scans for clinical indications. The remaining 117 infants had their first scan at age 7 - 10 days.

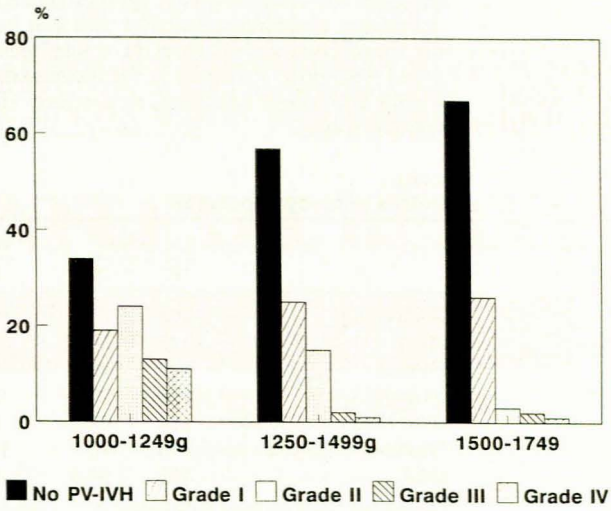

FIG. 1.
Prevalence and grading of PV-IVH by 250 g weight categories according to Papile *et al.*'s[14] classification.

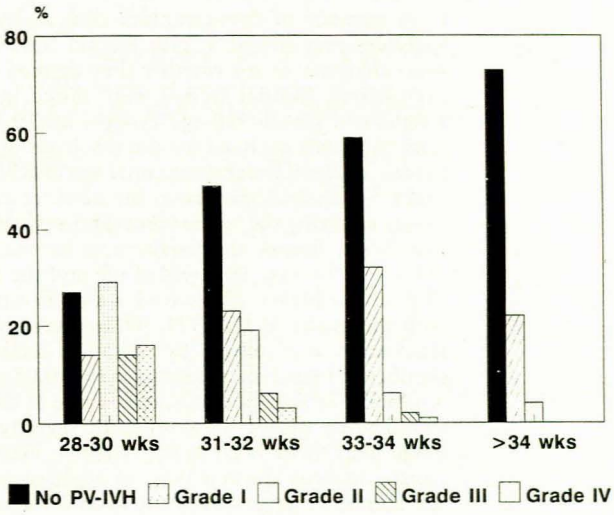

FIG. 2.
Prevalence and grading of PV-IVH by gestational age categories according to Papile *et al.*'s[14] classification.

Of the 282 study infants, 130 (46,1%) had ultrasound evidence of PV-IVH (Table I), but only 25 (8,9%) had moderate to severe haemorrhages (grades III or IV). Only 125 infants' mothers (44,3%) had attended antenatal clinics. Details of the sex and place of birth of the study infants and the prevalences of birth weight less than 1500 g, gestation less than 35 weeks and intra-uterine growth retardation are set out in Table I, with the overall prevalence of PV-IVH for each group. The prevalences of PV-IVH for infants weighing less than 1 500 g and infants born at less than 35 weeks' gestation were 53,3% and 52,1% respectively. Infants were divided into 250 g weight categories and also grouped according to gestational age. The distribution of the grades of PV-IVH by weight and gestational age categories is shown in Figs 1 and 2. As can be seen, the

overall prevalence and severity of PV-IVH decreased with increasing birth weight and gestation. Of infants weighing less than 1 250 g at birth, 66% had some grade of PV-IVH, compared with 43% of those weighing 1 250 - 1 499 g ($P < 0,01$) and 33% of those weighing 1 500 - 1 749 g ($P < 0,001$). The prevalence of moderate to severe PV-IVH (grades III or IV) was 24% for infants weighing less than 1 250 g at birth and 29% for those born at less than 31 weeks' gestation, compared with only 3% and 4% for those with higher birth weight and longer gestation, respectively ($P < 0,001$ for comparisons).

TABLE I.
Details of study population

	Total		With PV-IVH*	
	No.	%	No.	%
Total cohort	282		130	46,1
Male	142	50,3	70	49,3
Female	140	49,7	60	42,9
Inborn†	224	79,4	101	45,1
Birth weight < 1 500 g	184	65,2	98	53,3
Gestation < 35 wks	215	76,2	112	52,1
SGA	153	54,3	58	37,9

* Number and % with any grade of PV-IVH.
† Of the remaining infants 10 (3,5%) were born at a Soweto clinic, 14 (5,0%) at another hospital or clinic, and 34 (12,1%) at home or *en route* to Baragwanath Hospital.
There were no significant differences for overall prevalence or severity of PV-IVH according to sex or place of birth.

A number of demographic, clinical and laboratory variables recognised as risk factors for PV-IVH[3,15,20-22] were analysed to see whether they applied to our study population. Similar trends were noted in the various weight and gestational age groups, and the risk factors were therefore analysed for the whole group. In the univariate analysis, lower gestational age and birth weight, a lower 5-minute Apgar score, the need for active resuscitation at birth, the occurrence and severity of hyaline membrane disease, the requirement for mechanical ventilation in the first 48 hours of life and the development of pneumothorax all showed a significant correlation with the grade of PV-IVH, while intra-uterine growth retardation and delivery by caesarean section showed a significant negative correlation ($P < 0,05$ in all cases). 'Outborn' infants (see footnote, Table I) did not have a significantly higher occurrence or severity of haemorrhage than those born in the hospital. However, multivariate analysis showed that, in addition to gestational age and birth weight, only the need for active resuscitation at birth, the need for mechanical ventilation and the occurrence of pneumothorax were significantly associated with the development and severity of PV-IVH.

Survival of infants according to the occurrence of PV-IVH is shown in Table II. Survival decreased as the grade of PV-IVH increased, and this association was highly significant ($P < 0,001$). Only 4 infants with grade III PV-IVH and 1 with grade IV haemorrhage survived.

TABLE II.
Outcome according to grade of PV-IVH

Grade of PV-IVH	Total		Survived to hospital discharge	
	No.	%	No.	%
0	152	53,9	141	92,8
I	67	23,8	56	83,6
II	38	13,5	26	68,4
III	14	5,0	4	28,6
IV	11	3,9	1	9,1
Total	282	100	228	80,9

Ultrasound scanning-detected neuropathological sequelae of PV-IVH in the 228 surviving infants were also related to the grade of PV-IVH. Of the babies without PV-IVH the vast majority of survivors, 126 out of 141 (89%), had normal follow-up ultrasound scans at or close to 40 weeks' post-conceptual age. Of the surviving infants with grade I PV-IVH, 55% (31 out of 56) were found to have developed germinal matrix cysts on follow-up ultrasound scans, while cysts were found in only 9 out of 141 surviving infants (6%) with no record of PV-IVH. Approximately 50% of infants with intraventricular bleeding (grade II or more) developed some degree of ventricular enlargement if they survived the initial period, but only 6 of these infants developed clinical hydrocephalus. In 5 cases the hydrocephalus arrested spontaneously, while 1 surviving infant required a ventriculoperitoneal shunt for post-haemorrhagic hydrocephalus. Generally, ventricular dilatation appeared to reach a maximum between 1 and 2 weeks after the initial bleed and then to settle over the next 1 - 2 months. Five of the 141 infants with no previously documented intraventricular bleeding developed mild, non-progressive ventricular dilatation. Only 3 infants who survived to hospital discharge had definite cystic periventricular leucomalacia (2 of these had grade I and 1 had grade III PV-IVH originally). Periventricular leucomalacia (PVL) had also been noted in 6 of the 54 infants who died. Three of these infants had grade III haemorrhage and 3 had grade IV PV-IVH. The only surviving infant who developed a large porencephalic cyst[15] was the one who had sustained a grade IV haemorrhage and survived.

Discussion

The usual reported prevalence of PV-IVH in infants weighing less than 1 500 g at birth is 30 - 50%.[14-16,23,24] It would appear that the prevalence of PV-IVH in major centres has actually been decreasing over the last few years, in spite of the fact that survival rates for premature infants (particularly of those weighing less than 1 000 g at birth) are increasing, and the prevalence of PV-IVH is directly correlated with increasing prematurity. For example, Volpe's group[1] recently reported a PV-IVH prevalence of only 17% for infants with birth weights between 1 001 and 1 500 g, while Philip *et al.*[25] reported a prevalence of 25%. In both cases these were lower than previously reported figures from the same centres and it is probable that better perinatal care resulted in the reductions.

In this study the prevalence of PV-IVH of over 50% for infants weighing less than 1 500 g at birth and for those born at less than 35 weeks' gestation was higher than in most previously reported studies, all the more so because we did not include infants weighing less than 1 000 g at birth. While it is possible that this relatively high overall prevalence may in part have been due to overdiagnosis of subependymal (grade I) haemorrhages, accepted criteria for diagnosing these lesions were strictly adhered to. In addition, the fact that 55% of all infants with initial grade I haemorrhage went on to develop subependymal cysts suggests that they did indeed have a subependymal bleed. Over 50% of the women delivering VLBW infants at Baragwanath Hospital have not attended antenatal clinics, many women arrive at the hospital in advanced premature labour and deliver within a relatively short period of time, and the hospital is frequently overcrowded, so that VLBW infants with respiratory distress may have to wait longer than is desirable before being ventilated, owing to a shortage of ventilator facilities. We speculate that these factors all contribute to a compromise in the condition of many VLBW infants managed at the hospital and in turn result in the high prevalence of PV-IVH.

While the relatively high prevalence of PV-IVH at Baragwanath Hospital is of concern, the majority of haemorrhages that occurred in this study population were small. In this study, moderate or severe haemorrhage (grades III and IV) occurred in 12,0% of infants with birth weights of less than 1 500 g and in 11,6% of those born at less than 35 weeks' gestation, which is comparable with the reported rates of 6 - 19%.[24-26] As seen in Table II, the high prevalence of PV-IVH at Baragwanath Hospital is largely due to an excess of grade I and, to a lesser extent, grade II PV-IVH when compared with other reported studies. It has been suggested that risk factors for germinal matrix haemorrhage on the one hand and intraventricular haemorrhage on the other may differ,[27] and it is therefore possible that conditions in our study population favour the development of germinal matrix haemorrhage but not necessarily large intraventricular bleeds.

Multiple risk factors have previously been implicated in the causation of PV-IVH in VLBW infants.[3,15,20-22,26] The factors which had a significant association with PV-IVH in this study have been found previously. The significant association between the need for active resuscitation and PV-IVH, even when gestational age and the severity of lung disease were considered, suggests that prevention of birth asphyxia in these infants could result in a reduction in the prevalence of PV-IVH. The association between PV-IVH and outborn status has been reported consistently, but, somewhat surprisingly, this was not the case in this study despite the fact that 59% of the outborn infants were actually born at home or before arrival at Baragwanath Hospital. This paradoxical finding may relate to a selection process whereby only those VLBW infants born at home with less serious complications may have reached the hospital. Reported studies have shown intra-uterine growth retardation to be either protective or an additional risk factor for PV-IVH.[21,28] In the multiple linear regression analysis of our data, intra-uterine growth retardation was not a significant risk factor, but a more detailed analysis of this in our study population is being conducted.

In summary, there appears to be a high overall prevalence of PV-IVH, particularly smaller haemorrhages, in this study population. Some of the factors responsible should be preventable by the application of basic primary and secondary health care measures. With the anticipated improvement in these levels of health care, it will be important to monitor the prevalence of PV-IVH in institutions such as ours to see if the expected decline takes place.

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