Neonatal complications and risk of intraventricular-periventricular hemorrhage

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Summary: We have prospectively studied 117 premature infants ≤1500 gm (VLBW) to assess the relationship between maternal, obstetric, fetal and newborn complications and the grade of periventricular-intraventricular hemorrhage (PVH-IVH). PVH-IVH was documented by cranial ultrasonography in 41% of surviving neonates. 83% of infants with PVH-IVH grade I - II survived as compared to the 39% of infants with PVH-IVH grade III - IV ($p < .001$). Maternal and obstetric complications were not associated with PVH-IVH (NS). Newborn respiratory complications ($p < .00\,4$) and major infections ($p < .02$) are independent variables associated with PVH-IVH.

Immaturity at delivery, metabolic acidosis, respiratory distress syndrome and recurrent apnea are important mechanisms of cerebral injury contributing to severity of PVH-IVH.

Key words: Neonatal complications; Ventricular hemorrhage.

INTRODUCTION

Periventricular-intraventricular hemorrge (PVH-IVH) of preterm very low birthweight infants (VLBW: ≤1500 gm) is a major problem in modern obstetrics. The incidence rate of VLBW is 3% with an increased survival rate in the last few years, and evaluable in 70-95% of cases ([1, 2]). These infants are particulary exposed to adverse events that can directly or indirectely influence the central nervous system ([3]). The association between perinatal hypoxia and the subsequent development of PVH-IVH is generally accepted ([4]). PVH-IVH is therefore extremely important. It is found in 20-50% of VLBW ([5]).

Computerized tomography and ultrasound examinations in the newborn indicate that most PVH-IVH occurs in the first 3 days of life with 30% to 40% of cases occurring within 24 hours of delivery ([6, 7]). The bleeding usually originated from the capillaries in the germinal matrix which are not supported by firm glial structures surrounding larger vessels ([8]). The frequent instances of cerebral hemorrhage in premature infants are the result of the vulnerability of their capillaries to rises in arterial pressure resulting, in turn, from impaired autoregulation ([9]). Arterial pressure rises during motor activity, seizures, convulsions, respiratory distress or apnea ([9]).

This study examined the association between maternal, fetal, newborn complications, acid-base assessment and severity

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of intraventricular-periventricular hemorrhage in the preterm newborn infants ≤ 1500 gm.

MATERIALS AND METHODS

All live-inborn infants, between 24 and 37 weeks'gestation weighing from 500 to 1500 g were analyzed to assess the relationship between maternal, obstetric, fetal and newborn complications and intraperiventricular hemorrhage. The study was carried out from January 1986 to October 1991 at the Department of Obstetrics & Gynaecology of Parma (Italy), a referaal centre having more than 2000 deliveries each year and including 117 inborn infants. Gestational age was recorded as the last completed week, and was based on a routine ultrasonic examination performed in the 17th to 18th week of gestation. Every delivery was attended by a neonatologist and all infants had immediate neonatal resuscitation and intensive care. The clinical data for each case were obtained from the permanent computerized hospital records. The following maternal and obstetric complications were assessed for each obstetric patient, and included prior pregnancy wastage such as stillbirth and neonatal death in a previous pregnancy, hypertension in pregnancy (blood pressure >140/90 mmHg), maternal insulin-dependent diabetes.

Obstetric and gestational complications included antepartum hemorrhage due to placenta previa or abruptio placenta, premature rupture of membranes, chorioamnionitis (body T >38° C with leukocytosis and fetal tachycardia), isoxsuprine therapy for preterm delivery, multiple pregnancy, the respiratory distress syndrome prophylaxis conducted with 6 mg of dexamethasone intramuscularly every 12 hours for a total of 24 mg.

Labor complications included amniotic fluid meconium stained, abnormal fetal heart rate patterns including variable decelerations graded as (i) mild, when the duration is less than 30 seconds or the FHR (Fetal Heart Rate) does not fall below 80 bpm; (ii) moderate, when the level of FHR drops below 80 bpm regardless of the duration; (iii) severe, when the FHR drops below 70 bpm for more than 60 second; late decelerations, when the onset is late in the contraction cycle 30 seconds or more after the onset of the accompanying contraction; moderate (100 bpm <FHR <120 bpm) and severe (FHR <100 bpm) fetal bradycardia as well as moderate (160 bpm <FHR <180 bpm) and severe (FHR >180 bpm) fetal tachycardia or lack of heart variability (<2 bpm); breech presentation and cesarean section.

The neonatal characteristics and complications were Apgar score at 1 and 5 minutes, immaturity with an ultrasonographically documented gestational age; small for gestational age in which birth weight was less than the tenth percentile; respiratory distress syndrome (RDS) and newborn respiratory complications requiring O_2 therapy; major infections (septicemia or meningitis) defined by the isolation of a pathogenic microorganism in body fluid along with clinical signs as diagnosed by the neonatologist; newborn encephalopathy, defined as moderate in the presence of lethargy and hypotonia and severe in the presence of seizures and/or recurrent apnea. Survival was defined as surviving the 7 day neonatal period. Autopsy was performed in all infants who died. A blood sample from the umbilical artery was performed within the Ist hour of life in order to evaluate the neonatal acid-base status. The diagnosis of metabolic acidosis was assessed using the following parameters: pH <7.20, buffer base (BB) <34 mmol/l, base excess (BE) < -12 mmol/l, base excess extracellular fluid < -8 mmol/l. Intracranial hemorrhage was then graded as follows: subependimal (Grade I); intraventricular, normal ventricular size (Grade II); intraventricular, increased ventricular size (Grade III); intraventricular, parenchymal extension (Grade IV) ([10]). Severe intraventricular hemorrhage was defined as those associated with a grade III or IV hemorrhage.

Diagnosis of PVH-IVH was made by cerebral ultrasound examinations performed between day 1 and day 4 after birth, on day 7, at discharge, using a 5 MHz transducer placed on the anterior fontanelle to obtain a series of sagittal and coronal images.

The index group included 57 preterm infants with intraperiventricular hemorrhage and according to the above grading system we found 29 infants with minor lesions (Grade I-II) and 28 with major lesions (Grade III-IV).

The control group included 50 preterm surviving infants with weights ranging from 500 to 1500 g and with no ultrasonographically documented PVH-IVH.

Ten infants with no PVH-IVH had neonatal deaths and so they have not been included in the study. A preliminary statistical evaluation of the relationship between maternal, obstetric and fetal-newborn complications was carried out with the use of a two-way cross-tabulation and χ^2 analysis. This latter identified the independent variables appropriate for multivariate examination. The logistic regression analysis was used to assess the mutivariate association of the previous significant independent variables.

RESULTS

The maternal and obstetric complication did not demonstrate an independent association with PVH-IVH.

Nine neonatal variables, small for gestational age, recurrent apnea, seizures, major infections, respiratory distress syndrome and O_2 therapy, pH < 7.20, BB <34.0 and BEecf < − 8.0 demonstrated a significant association with periventricular-intraventricular hemorrhage when compared with control group (Tab. 1).

The logistic regression analysis used to examine the multivariate associations of the significant independent variables indicates that only major infections ($p<.02$) and newborn respiratory complications ($p<.02$) and newborn respiratory complications ($p<.004$) are independent variables associated with intracranial hemorrhage (Table 2).

Intra-periventricular hemorrhage (PVH-IVH) occurred in 57 (49%) cases of overall VLBW and accounted for 41% in surviving infants. The survival rate (83%) of newborn infants with a minor grade of PVH-IVH was statistically significant when compared to those with major lesions (39%) (delta=44, $p<.001$). (Table 3).

A statistical difference for pH and BE between surviving and dead newborns with PVH-IVH has been pointed out (Tab. 4).

Data from the neonatal acid-base assesment showed that acidosis is statistically significant in infants with minor (grade I - II) and major lesions (grades III - IV) of PVH-IVH when compared with control group (Table 5).

The relationship between neworn complications and intracranial hemorrhage is shown in Table 6.

Of the 43 cases of respiratory distress spndrome, 31 (72%) demonstrated an association with PVH-IVH: 12 (39%) in newborns with PVH-IVH I - II and 19 (61%) in those with PVH-IVH III - IV

Table 1. — *Neonatal complications in newborns with PVH-IVH as compared with control group.*

Complications	PVH-IVH (N=57)	CG (N=50)	p
SGA	17	31	p<.001
R. Apnea	25	8	p<.01
Seizures	16	2	p<.001
Major Infect.	13	3	p<.05
RDS	31	9	p<.001
O_2 therapy	52	25	p<.001
pH <7.20	32	18	p<.05
BB <34.0	49	32	p<.01
BEecf <−8.0	26	10	p<.01

Table 2. — *Logistic regression analysis of relationship of newborn complications to PVH-IVH.*

Complications	χ^2	p
Respiratory complications	7.96	.004
Major infections	4.89	.02

Table 3. — *The survival rate of newborns with PVH-IVH Grade I-II vs. PVH-IVH Grade III-IV is statistically significant for a p<.001.*

	Birthweight (gm)		Tot.	Surviving	
IVH	<1000	1000-1500		No.	%
Minor					
Grade I	4	7	11	9	82
Grade II	9	9	18	15	83
Major					
Grade III	3	6	9	6	66
Grade IV	9	10	19	5	26

Table 4. — *Acid-base assessment in surviving and dead newborns with PVH-NVH.*

	PVH-IVH Survived (N=35)	PVH-IVH Dead (N=22)	p
pH <7.20	16	16	p<.05
BB <34.0	31	18	NS
BE <−12.0	1	8	p<.001
BEecf <−8.0	14	12	NS

Table 5. — *Acid-base assessment in newborns with PVH-IVH I-II (Group I), PVH-IVH III-IV (Group II) and control (Group III). Enclosed in round brackets are groups with a statistically significant difference.*

	PVH-IVH I-II (N=29)	PVH-IVH III-IV (N=28)	CG (N=50)
pH <7.20	16	16	16
BB <34.0	26	23	29
BB <−12.0	3	6	0 (I, II)
BEecf <−8.0	12	14	10 (I, II)

BE: I vs. III $p<.05$
II vs. III $p<.001$
Beecf: I vs. III $p<.01$
II vs. III $p<.01$

Table 6. — *Relationship between neonatal complications and the grades of PVH-IVH.*

	Tot. VLBW (N=117)	Grade I-II PVH-IVH	Grade III-IV PVH-IVH
PVH-IVH	57 (49%)	29 (51%)	28 (49%)
RDS	43 (37%)	12 (39%)	19 (61%)*
R. Apnea	39 (33%)	7 (28%)	18 (72%)**
Seizures	24 (20%)	5 (31%)	11 (69%)
O_2 therapy	83 (71%)	24 (47%)	27 (53%)
Major infect.	16 (14%)	8 (61%)	5 (39%)

(*) $p<.05$
(**) $p<.01$

($p<.05$). The use of antenatal corticosteroids in these infants not only resulted in a substantial reduction in the incidence of RDS from 42% to 21% ($p<.05$), but the infants so treated had a lower incidence of severe PVH-IVH from 59% to 9% ($p<.01$).

Of the 39 cases of recurrent apnea, 25 (64%) demonstrated an association with PVH-IVH: 7 (28%) in infants with PVH-IVH I - II, 18 (72%) in those with PVH-IVH III - IV ($p<.01$).

Neonatal seizures occurred in 24 infants, 16 (66%) had intracranial hemorrhage: 5 (31%) in newborns with PVH-IVH I - II and 11 (69%) in infants with PVH-IVH III - IV (NS).

Of the 83 (71%) infants with respiratory complications who underwent O_2 therapy, 51 (61.4%) had intracranial hemorrhage: 24 (47%) in newborns with PVH-IVH I - II and 27 (53%) in infants with PVH-IVH III - IV (NS).

Major newborn infections such as septicemia and meningitis were documented in 16 patients and 13 (81%) had an association with PVH-IVH: 8 (61%) in newborn infants with grade I - II and 5 (39%) in newborns with grade III - IV (NS).

The gestational age and birthweights registered in newborns with PVH-IVH I - II and PVH-IVH III - IV showed a statistical difference between newborns with PVH-IVH I - II and PVH-IVH III - IV as compared with control group (Table 7).

COMMENT

The incidence rate of intracranial hemorrhage of 41% in surviving preterm newborn infants ≤1500 gm was in agreement with many recent reports ([11, 12, 13, 14]).

Furthermore, the incidence of intracranial hemorrhage was 68% in surviving infants with less severe PVH-IVH (grade I - II) and was 32% in those with severe PVH-IVH (grade III - IV). The survival rate of overall VLBW accounted for 73% with a remarkable incidence in newborn

Table 7. — *Gestational age and birthweight in newborn with PVH-IVH I-II (Group 1), PVH-IVH III-IV (Group II) and control (Group III). Enclosed in round brackets are groups with a statistical difference of $p<.001$.*

	PVH-IVH I-II (Mean±SD)	PVH-IVH III-IV (Mean±SD)	CG (Mean±SD)
Gest. age	29.3±2.4	28±2.16	32.7±2.9 (I, II)
Birthw.	1048.8±235.6	995±199.8	1265.7±200.1 (I, II)

infants with minor grade PVH-IVH as compared with major grade (83% vs 39%) ($p < .001$).

The maternal and obstetric complications that usually define the high-risk pregnancy were analyzed in this study and none were independently associated with intracranial hemorrhage. Of the significant newborn complications associated with intracranial hemorrhage on univariate analysis, only RDS major infections demonstrated an independent association with intracranial hemorrhage on subsequent multivariate analysis. Therefore, the use of antenatal dexamethasone resulted in a statisticaly reduction of RDS from 42% to 21% ($p < .05$) and of severe grades of PVH-IVH from 59% to 9% ($p < .01$). The neonatal survival rate was dependent not only on the grade of intracranial hemorrhage but also on the degree of newborn metabolic acidosis.

Our analysis of acid-base assessment showed a clear association between metabolic acidosis and major lesions of intracranial hemorrhage confirming acidosis as a mediator of several events leading to intracranial hemorrhage. This association was not present in preterm infants with minor lesions of PVH-IVH or in those < 1000 g, emphasizing the role of immaturity in the occurrence of PVH-IVH.

Analysis of the mean and the standard deviation of birthweight and gestational age or newborns with either PVH-IVH I - II or PVH-IVH III - IV suggest that a statistically significant difference can be observed between newborns with intracranial hemorrhage and the control group. The ratio of neonatal complications to incidence of the grades of intracranial hemorrhage suggest that only RDS and recurrent apnea are statistically significant in newborns with PVH-IVH III - IV as compared to those with PVH-IVH I - II.

When asphyxia is considered, differences can be found between newborns with minor and major lesions of intracranial hemorrhage. This suggests that minor lesions of IVH can almost be considered as a condition partly due to immaturity or to an insufficent autoregulation of cerebral blood flow. The delicate and unstable homeostasis of VLBW can be worsened by asphyxia especially if severe.

This condition can lead to the major lesions of intracranial hemorrhage that are characterized by a different and worsening neonatal outcome.

REFERENCES

1) Thompson T., Reynolds J.: "The results of intensive care therapy for neonates. I) Overall neonatal mortality rates; II) Neonatal mortality rates and long term prognosis for birth weight neonates". *J. Perinat. Med.*, 1977, *5*, 59.
2) Ferrari B., Tonni G., Balduzzi L., Grignaffini A.: "The increased survival rate of the preterm: role of intracranial hemorrhage". *J. Foet. Med.*, 1989, *3-4*, 57.
3) Luthy D. A., Kirkwood K.: "Status of infants at birth and risk factors for adverse neonatal events and longterm sequelae: a study in low birth weight infants". *Am. J. Obst. Gyn.*, 1987, *157*, 676.
4) Volpe J. J.: "Intraventricular hemorrhage in the premature infant-current concepts". *Part. 1 Ann. Neurol.*, 1989, *3*, 33.
5) Kuban K. C. K., Skouteli H., Cherer A.: "Haemorrage, phenobarbital and fluctuating cerebral blood flow velocity in the neonate". *Pediatrics*, 1988, *82*, 548.
6) Szymonowicz W., Yu V. Y.: "Timing and evolution of periventricular hemorrhage in infants weighing 1250 Gm or less at birth". *Arch. Dis. Child.*, 1984, *59*, 1.
7) Rumack C. M., Manco-Johnson M. L.. Manco-Johnson M. J. *et al.*: "Timing and course of neonate intracranial hemorrhage using real-time ultrasound". *Radiology*. 1985, *154*. 101.
8) Hambleton G., Wigglesworth J.S.: "Origin of intraventricular hemorrhage in the preterm infant". *Arch. Dis. Childhood*, 1976, *51*, 651.
9) Lou H. C., Lassen N. A., Friis-Hassen B.: "Is arterial hypertension crucial for the development of intraventricular hemorrhage in the premature infants?". *The lancet June 9*, 1215.
10) Papile L., Burstein R., *et al.*: "Incidence and evolution of subependymal and intra-

ventricular hemorrhage: a study of infants with birth weights less than 1500 grams". *J. Pediatr.,* 1978, *92,* 529.

11) Thorburn R. J., Lipscomb A. P., Reynolds E. O.: "Accuracy of imaging of the brains of newborn infants by linear-array real-time ultrasound". *Early Hum. Dev.,* 1982, *6,* 31.

12) Kosmetatos N., Dinter P., Williams M. L. *et al.:* "Intracranial hemorrhage in the premature: its predictive features and outcome". *Am. J. Dis. Child.,* 1980, *134,* 855.

13) Bada H. S., Korones S. B., Anderson G. D. *et al.:* "Obstetric factors and relative risk of neonatal germinal layer/intraventricular hemorrhage". *Am. J. Obst. Gyn.,* 1984, *148,* 798.

14) Low J. A., Galbraith R. S., Sauerbrei E. E. *et al.:* "Maternal, fetal, and newborn complications associated with newborn intracranial hemorrhage". *Am. J. Obst. Gyn.,* 1986, *154,* 345.

15) Ferrari B., Luzietti R., Tonni G.: "PVH-IVH in relation to fetal-newborn metabolic acidosis". *J. Foet. Med.,* 1990, *1-4,* 59.

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