Acta Biomed 2022; Vol. 93, N. 2: e2022041 DOI 10.23750/abm.v93i2.11187

Original article

Intraventricular hemorrhage in preterm newborn: Predictors of mortality

Benedetta Piccolo[1], Mariacristina Marchignoli[2], Francesco Pisani[3]

[1]Child Neuropsychiatry, Mother and Child Department, University Hospital of Parma, Parma, Italy; [2]Child Neuropsychiatry, Dipartimento Assistenziale Integrato Salute Mentale Dipendenze Patologiche, Fidenza, Parma, Italy; [3]Child Neuropsychiatry, Department of Medicine and Surgery, University of Parma, Parma, Italy

Abstract. *Background and aim*: Intraventricular hemorrhage (IVH) is a cause of morbidity and mortality in preterm infants. It occurs primarily in preterm newborns with an incidence of about 20% and, despite the evolution of neonatal care that allows more and better survival, continues to be a cause of morbidity and mortality in all intensive care units. Our research aimed to evaluate the independent risk factors of mortality and the relative odds ratio for each degree of IVH. *Methods*: In this retrospective study were included 96 preterm infants, born between 23^ and 36^ weeks of gestational age, which developed IVH of degree two-three-four diagnosed by means of cranial ultrasound. It was made a comparison within the sample by distinguishing the group with IVH degree two from degree three and four. *Results*: IVH of degree three and four was independently associated with mortality. We found a higher number of deaths in the GAs <= 26 weeks (p <0.01), which was also an independent predictor of mortality. *Conclusion*: With this study it was further highlighted the high mortality of patients with an elevated degree of IVH and low birth weight and early gestational age. These data, of important clinical relevance, oblige us to find new therapeutic strategies aimed at reducing the serious consequences of that disease. (www.actabiomedica.it)

Key words: intraventricular hemorrhage, preterm infants, mortality

Introduction

Intraventricular hemorrhage (IVH) occurs primarily in preterm newborns with an incidence of about 17.0% for grade one, 12.1% for grade two, 3.3% for grade three, and 3.8% for grade four (1), and, despite the evolution of neonatal care that allows more and better survival, continues to be a significant cause of morbidity and mortality (2). Anatomical, vascular, hemodynamic and extra-vascular factors, infections, mechanical ventilation, lack of clotting factors, increased fibrinolytic activity of the germinal matrix, are the main factors implicated in the genesis of IVH (3,4). Cranial ultrasound is the most used imaging technique for the first screening of cerebral lesions in newborns and Papile's classification of the IVH is the most used (5). This classification is useful to better assess the phenomenon and predict outcome both during the neonatal period and during the follow up (6). The prognosis for IVH of degree one is good; in those patients with an IVH of 2nd degree there is an expected mortality of 10% and of hydrocephalus in 20%, while for IVH of 3rd degree the mortality ranges from 20 to 50% and the incidence of hydrocephalus from 50 to 80% of subjects (2). Recently, this trend in which the risk of death increases in association with the grade of IVH has been confirmed (7); the overall risk of mortality was similar in infants either with (4-7%) or without IVH of grade one (10%), and it was significantly greater in infants with higher value of IVH, specifically: 8-10% in IVH of grade two, 18 % in those with grade three and about 40% in the IVH

of grade four (7,8). Our research aimed to evaluate the independent risk factors of mortality and the relative odds ratio for each degree of IVH.

Subjects and methods

In this retrospective study ninety-six preterm infants were included, born between 23^ and 36^ weeks of gestational age (GA), consecutively admitted at the NICU of the Parma University Hospital between 1995 and 2004, which developed IVH of degree two-three-four diagnosed by means of cranial ultrasound and graded according to Papile's classification (5). Many diagnoses were confirmed by using brain CT or MRI because some findings were better depicted, although not routinely employed in the initial evaluation (9). The variables used in this study include GA, sex, mode of delivery, twins, the use of resuscitation maneuvers, birth weight, Apgar score at the first and fifth minute, degree of IVH, and mortality evaluated at discharge.

The study was approved by the Local Ethics Committee (n°26204) of Parma University Hospital.

Statistical analysis

Continuous variables were compared using the Student T-test and/or the Mann-Whitney U test.

The frequency data were analyzed by the X^2 test and/or the exact probability test of Fisher.

It was made a comparison by distinguishing a cohort of patients with an IVH of grade two versus the others with a higher degree of IVH. To evaluate the independent risk factors of death the multiple logistic regression (stepwise method) was used. Statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS, version 14.0).

Results

The characteristics of the sample clinical findings and results are summarized in Table 1.

IVH of degree three and four were independently associated with mortality with an OR respectively increasing from 6.822 to 19.584 (Table 2).

Of the ninety-six infants studied, fifty-three died before discharge (55.2%).

Introducing the cut-off of 26 weeks of GA (median value of the two groups) we found a higher number of deaths in the GAs <= 26 weeks (p <0.01), which was also an independent predictor of mortality with an OR of 3.761.

Discussion

The intraventricular hemorrhage is one of the major complications of preterm births and, although its incidence is decreasing thanks to the evolution of neonatal intensive care, it brings a crucial impact on

Table 1. Characteristics of the sample clinical findings and results

Variable	All Subjects	Survivors Dead		p
Total	96	43 (44.8%)	53 (55.2%)	
Gender				ns
Male Female	60 (62.5%) 36 (37.5%)	27 (45%) 16 (44.4%)	33 (55%) 20 (55.5%)	
Mode of delivery				
Spontaneous Caesarean section Twins	51 (53.1%) 45 (46.9%) 21 (21.9%)			
Gestational Age (GA)				**< 0.01**
> 26	41 (42.7%)	25 (60.9%)	16 (39%)	
≤ 26	55 (57.3%)	18 (32.7%)	37 (62.7%)	

Variable	All Subjects	Survivors Dead		p
Birth weight				**= 0.001**
>1000 g	28 (29%)	21 (75%)	7 (25%)	
<=1000 g	68 (71%)	23 (33.8%)	45 (66.2%)	
1-min Apgar score				**< 0.01**
> 5	15 (15.6%)	12 (80%)	3 (20%)	
<= 5	79 (82.3%)	30 (38%)	49 (62%)	
5-min Apgar score				**< 0.05**
> 7	12 (12.5%)	7 (58.3%)	5 (41.7%)	
6-7	32 (33.3%)	20 (62.5%)	12 (37.5%)	
<= 5	39 (40.6%)	12 (30.8%)	27 (69.2%)	
Reanimation maneuvers				ns
Yes	89 (93%)			
No	7 (7%)			
IVH				**< 0.001**
2°	41 (42.7%)	28 (68.3%)	13 (31.7%)	
3°	35 (36.5%)	11 (31.4%)	24 (68.5%)	
4°	20 (20.8%)	4 (20%)	16 (80%)	

Table 2. Odds ratio of IVH of degree three and four

	O. R.	95% C. I.	p
IVH			0.001
IVH (3)	**6.822**	1.975-23.785	0.003
IVH (4)	**19.584**	3.564-107.598	0.001
E.G. (<=26)	**3.761**	1.237-11.436	0.020

outcome (7,8). The pathogenesis of IVH in the germinal matrix is multifactorial and closely related to bleeding disorders, provoked by changes in microvascular pressure. The outcome is well correlated with the severity of the bleeding and, in particular, with the extension of the parenchymal involvement (4,8,10). The median incidence of severe intraventricular hemorrhage decreased from 9.4% in 2005 to 7.9% in 2014 (11). In another study a grade IV of IVH was described in approximately 10%-15% of infants (12).

In a series of 6638 preterm infants, it has been reported that only 13.6% had severe IVH (13) while others have estimated that the incidence of each degree of IVH in preterm infants weighing less than 1500 grams was 10% for IVH of degree one-two, 6% for degree three and 4% for degree four (6). In a more recent study IVH is described to occur in 25% to 30% of all very low birth weight preterm infants, 1500 g, and the reported incidence in extremely low birth weight infants, 1000 g, is as high as 45% (14). The mortality rate seems to be decreased over time from 17.4% during 1993–1997 to 7.7% during 2008–2010, but mortality in IVH of degree four has not changed significantly, being around 40% (7,8), similar to earlier study (15,16,17). However, higher mortality rates have been reported (18,19). In our study, the IVH of degree two was the most frequent (41/96; 42.7%), whereas 36.5% presented an IVH of third degree and only 20.8% of degree four. These data correspond with that presented in other studies (2,6,20,21).

In our sample the prevalence of deaths was 55.2% (53 of 96 infants) and all patients died before discharge with the degree of IVH proved to be significantly related to mortality (p <0.001).

This study highlights that severe degrees of IVH are independent predictors of high risk of mortality and the risk for each degree of IVH was separately considered. In fact, those patients with an IVH of degree four have an OR three times higher than those with an IVH of third degree (OR of IVH degree 4 = 19.584 vs OR of IVH degree 3 = 6.822). To our knowledge, these results with a stratified OR according to the different degree of IVH have not been evaluated so far (6,22,23,24).

IVH of degree three and four are often reported combined as "severe" IVH (14), despite different involvement of the periventricular zone and of the parenchyma, and with different long-term neurodevelopmental outcome. For example, neurologic morbidity approximates 35% in IVH of grade three germinal matrix-intraventricular hemorrhage but can reach 90% in those patients with periventricular hemorrhagic infarction (17,25). Only early GAs and low birthweight seem to be significant risk factors for severe IVH (25). However, it is still unknown if grade three and grade four of IVH have different risk factors and short-term morbidities (25). In our study only the extreme GA was a significant risk factor for IVH of grade four.

As mentioned before, the association between the different degrees of IVH and mortality was reported to be about 30-40% (17,26); while the extension of the IVH does not result to be related to mortality (26).

In our series, we found a relation between gestational age, birth weight, degree of IVH, Apgar score and mortality rate as previously reported (23,27,28). The higher number of deaths was seen in the extreme GAs <= 26 weeks ($p < 0.01$), which is also an independent predictor of mortality with an OR of 3.761. Besides earlier GAs, small birth weight for gestational age and low Apgar score at 5 minutes increased the odds of neonatal death in those infants with IVH of grade three.

With this study it has been highlighted how low birthweight and extreme GAs are independent risk factors for severe IVH, and this in turn is strongly related to a high risk of mortality. These data oblige us to find out a positive solution to this dramatic clinical condition that bears either significant health care costs and deep suffering to the families.

Conflict of Interest: Each author declares that he has no commercial associations (e.g. consultancies, stock ownership, equity interest, patent/licensing arrangement, etc.) that might pose a conflict of interest in connection with the submitted article.

References

1. Chevallier M, Debillon T, Pierrat V, et al. Neurodevelopment EPIPAGE 2 Writing Group. Leading causes of preterm delivery as risk factors for intraventricular hemorrhage in very preterm infants: results of the EPIPAGE 2 cohort study. Am J Obstet Gynecol 2017; May; 216(5): 518.e1-518.e12.
2. Owens R. Intraventricular hemorrhage in the premature neonate. Neonatal Netw 2005; May-Jun; 24(3): 55-71.
3. Robinson S. Neonatal posthemorrhagic hydrocephalus from prematurity: pathophysiology and current treatment concepts A review. J Neurosurg Pediatrics 2012; 9: 242–258.
4. Ballabh P. Intraventricular hemorrhage in premature infants: mechanism of disease. Pediatr Res 2010; Jan; 67(1): 1-8.
5. Papile LA, Burstein J, Burstein R, et al. Incidence and evolution of subependymal and intraventricular hemorrhage: a study of infants with birth weights less than 1,500gm. J Pediatr 1978; 92: 529-534.
6. Allan WC, Sobel DB. Neonatal intensive care neurology. Semin Pediatr Neurol 2004; Jun; 11 (2): 119-28.
7. Radic JA, Vincer M, McNeely PD. Outcomes of intraventricular hemorrhage and post hemorrhagic hydrocephalus in a population-based cohort of very preterm infants born to residents of Nova Scotia from 1993 to 2010. J Neurosurg Pediatr 2015; Jun; 15(6): 580-8.
8. Novak CM, Ozen M, Burd I. Perinatal Brain Injury: Mechanisms, Prevention, and Outcomes. Clin Perinatol 2018; Jun;45(2): 357-375.
9. Sanapo L, Whitehead MT, Bulas DI, et al. Fetal intracranial hemorrhage: role of fetal MRI. Prenat Diagn 2017; Aug; 37(8): 827-836.
10. Roland EH, Hill A. Germinal matrix-intraventricular hemorrhage in the premature newborn: management and outcome. Neurol Clin 2003; Nov; 21(4): 833-51.
11. Horbar JD, Edwards EM, Greenberg LT, et al. Variation in Performance of Neonatal Intensive Care Units in the United States. JAMA Pediatr 2017; Mar 6;171(3): e164396. (Erratum in: JAMA Pediatr 2017 Mar 1;171(3): 306.
12. Cizmeci MN, Linda S. de Vries, Linh G. Ly, et al. Periventricular Hemorrhagic Infarction in Very Preterm Infants: Characteristic Sonographic Findings and Association with Neurodevelopmental Outcome at Age 2 Years. J Pediatr 2020; 217: 79-85.
13. Goldstein RF, Cotten CM, Shankaran S, et al; Eunice Kennedy Shriver National Institute of Child Health and Human Development Neonatal Research Network. Influence of gestational age on death and neurodevelopmental outcome in premature infants with severe intracranial hemorrhage. J Perinatol 2013 Jan; 33(1): 25-32.
14. Mukerji A, Shah V, Shah PS. Periventricular/Intraventricular Hemorrhage and Neurodevelopmental Outcomes: A Meta-analysis. Pediatrics 2015; Dec; 136(6): 1132-43.
15. Bassan H, Feldman HA, Limperopoulos C, et al. Periventricular hemorrhagic infarction: risk factors and neonatal outcome. Pediatr Neurol 2006; Aug; 35(2): 85-92.
16. Brouwer A, Groenendaal F, van Haastert IL, et al. Neurodevelopmental outcome of preterm infants with severe intraventricular hemorrhage and therapy for post-hemorrhagic ventricular dilatation. J Pediatr 2008; May; 152(5): 648-54.

17. de Vries LS, Roelants-van Rijn AM, Rademaker KJ, et al. Unilateral parenchymal hemorrhagic infarction in the preterm infant. Eur J Paediatr Neurol 2001; 5: 139-49.
18. Hamrick SE, Miller SP, Leonard C, et al. Trends in severe brain injury and neurodevelopmental outcome in premature newborn infants: The role of cystic periventricular leukomalacia. J Pediatr 2004; 145: 593-9.
19. Futagi Y, Toribe Y, Ogawa K, et al. Neurodevelopmental outcome in children with intraventricular hemorrhage. Pediatr Neurol 2006; 34: 219-24.
20. Fernell E, Hagberg G, Hagberg B. Infantile hydrocephalus epidemiology: an indicator of enhanced survival. Arch Dis Child 1994; 70: 123-128.
21. Ward RM, Beachy JC. Neonatal complications following preterm birth. BJOG 2003; Apr; 110 Suppl20: 8-16.
22. Volpe JJ. Neurology of the Newborn. 4th ed. Philadelphia: Saunders, 2001:pp.428-493.
23. Kazan S, Gura A, Ucar T, et al. Hydrocephalus after intraventricular hemorrhage in preterm and low-birth weight infants: analysis of associated risk factors for ventriculoperitoneal shunting. Surg Neurol 2005; 64Suppl 2: 77-81; discussion S81.
24. Tillmann BU, Emons D, Bartmann P, et al. Posthemorrhagic unilateral hydrocephalus: fenestration of septum pellucidum as an alternative to shunt implantation. J Pediatr 2004 Jan; 144 (1): 126-8.
25. Sarkar S, Bhagat I, Dechert R, et al. Severe Intraventricular Hemorrhage in Preterm Infants: Comparison of Risk Factors and Short-Term Neonatal Morbidities between Grade 3 and Grade 4 Intraventricular Hemorrhage. Am J Perinatolol 2009; Jun; 26(6): 419-24.
26. Roze E, Kerstjens JM, Maathuis CG, et al. Risk factor for adverse outcome in preterm infant with periventricular hemorrhagic infarction. Pediatrics 2008; Jul; 122(1): e46-52.
27. Tsou KI, Tsao PN; Taiwan Infant Development Collaborative Study Group.
28. The morbidity and survival of very-low-birth-weight infants in Taiwan. Acta Paediatr Taiwan 2003; Nov-Dec;44(6): 349-55.
29. Handley SC, Passarella M, Lee HC, Lorch SA. Incidence Trends and Risk Factor Variation in Severe Intraventricular Hemorrhage across a Population-Based Cohort. J Pediatr 2018; September; 200: 24–29.e3.

Correspondence
Received: 29 December 2020
Accepted: 12 January 2021
Dr. Benedetta Piccolo
Child Neuropsychiatry, Mother and Child Department,
University Hospital of Parma,
via A. Gramsci 14, 43126
Parma, Italy
E-mail: benedetta.piccolo@gmail.com