Intraventricular hemorrhage in preterm newborn: Predictors of mortality

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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 23⁰ and 36⁰ 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 X² test and/or the exact probability test of Fisher.

**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

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

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

| IVH          | O. R. | 95% C. I.  | p        |
|--------------|-------|------------|----------|
| IVH          | 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).

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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.

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