Predictors of severe intraventricular hemorrhage in preterm infants under 29-weeks gestation

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ABSTRACT

Purpose: Preterm infants <29 weeks of gestation are at risk for severe intraventricular hemorrhage (IVH). Lower gestational age, birth weight, severe illness, as indexed by higher Score for Neonatal Acute Physiology - Perinatal Extension II (SNAPPE-II) are associated with severe IVH. The role of coagulation abnormalities on the first day after birth in severe IVH remains controversial. The present study investigated factors that predict the risk of severe IVH, including SNAPPE-II at 12 h and coagulation parameters on the first day after birth.

Materials and methods: A retrospective chart review of infants <29 weeks of gestation from January 2008 to December 2013 was performed. Prenatal and postnatal characteristics, SNAPPE-II at 12 h, coagulation parameters [prothrombin time (PT), INR, partial thromboplastin time (aPTT), thrombin time (TT), and fibrinogen] on the first day and cranial ultrasound examination records were collected. The association between clinical and laboratory variables and severe IVH was determined. A joint predictive model for the risk of severe IVH (grades 3 and 4) versus no-mild IVH (grades 0, 1, and 2) was developed using multiple regression analysis.

Results: Preterm infants of gestational age <29 weeks were included (n = 101). Fifteen (15%) infants had severe IVH. Lower gestational age (p = .006), birth weight (p = .008), African American race (p = .031) and higher SNAPPE-II at 12 h (p = .001) were associated with severe IVH. Infants with severe IVH had longer PT (p = .004), higher INR (p = .004) and lower platelet count (p = .034) than those with no-mild IVH. Stepwise logistic regression showed that only SNAPPE-II at 12 h was an independent predictor of severe IVH. For each unit increase in SNAPPE-II, the log odds of severe IVH increased by 0.045 (95% CI: [0.017, 0.073]; p = .002). A threshold of 55 on the SNAPPE-II yielded a sensitivity of 60% (9/15), a specificity of 91% (78/86), a positive predictive value (PPV) of 53% (9/17) and a negative predictive value (NPV) of 93% (78/84). All other demographic and clinical variables and coagulation abnormalities had an insignificant coefficient (p > .05) when included in a bivariate logistic model with SNAPPE-II.

Conclusion: SNAPPE-II at 12 h after birth is an independent predictor of severe IVH in preterm infants with gestational age <29 weeks.

Introduction

Preterm infants <29 weeks of gestation are at increased risk for developing severe intraventricular hemorrhage (IVH). A highly vascular subependymal germinal matrix, poorly supported immature vasculature, along with fluctuations in cerebral blood flow predisposes these infants to IVH [1–4]. Approximately 90% of IVH occurs within 72 h after birth [5–7]. Severe IVH is associated with a higher risk of mortality and morbidity, including hydrocephalus and seizures in the short term, and cerebral palsy, hearing and vision deficits, and learning disabilities in the long term [7–11]. Advances in neonatal care over the past two decades have improved survival of the preterm infants without impacting the prevalence of severe IVH [12]. A better understanding of the responsible factors is necessary for counseling parents and devising neuroprotective strategies. Score for Neonatal Acute Physiology – Perinatal Extension II (SNAPPE-II) is an internationally validated scoring method designed to...
predict the risk of morbidity and mortality in term and preterm newborn infants during hospitalization [13]. The score evaluates illness severity using 9 physiological and laboratory parameters collected within the first 12 h of birth. SNAPPE-II ranges from 0 to 162 with higher scores indicating a greater risk of mortality and morbidity. Although there is an association between higher SNAPPE-II (>45) and IVH [14], SNAPPE-II has not been used to predict the risk of IVH in an individual infant.

The role of coagulation abnormalities in severe IVH remains poorly understood, with some studies demonstrating an association and others not [15–18]. Coagulation parameters are determined in preterm infants considered to be at risk for IVH in some neonatal intensive care units (NICUs) [19], including ours, and abnormal results ("Laboratory Coagulopathy") are treated using blood products [20], although there are no evidence-based guidelines for either practice. The aim of the present study was to investigate whether coagulation abnormalities on the first day after birth could be used to predict the risk of severe IVH in preterm infants < 29 weeks, either by themselves or in combination with SNAPPE-II.

Materials and methods

Study population

A retrospective chart review was performed. Study participants were preterm infants < 29-weeks gestation born between January 2008 and December 2013 and admitted to the NICU at Hennepin County Medical Center (HCMC) in Minneapolis, MN, USA. Those included had complete data to calculate SNAPPE-II and coagulation parameters. Neonates were excluded if they had missing coagulation profiles or died before obtaining a cranial ultrasound. The study was approved by the institutional review boards at HCMC and the University of Minnesota.

Measurements

Neonatal data were abstracted from the electronic medical records. The data abstracted included basic demographic characteristics (gestational age, birth weight, sex, race, mode of delivery, maternal age, Apgar score at 5 min and antenatal steroid use), coagulation parameters (prothrombin time (PT, sec), international normalized ratio (INR), activated partial thromboplastin time (aPTT, sec), thrombin time (TT, sec), fibrinogen level (mg/dL) and platelet count (10^9/ml) on the first day of birth, SNAPPE-II components during the first 12 h after birth, and the presence and severity of IVH on ultrasound reports.

Coagulation parameters

Coagulation parameters were determined at a mean ± SD age of 4.06 ± 2.18 h. Coagulation parameters were determined in 1.8 ml heparin-treated blood samples drawn from a central arterial or venous catheter and analyzed using an ACL Top coagulation analyzer (Instrumentation Laboratory). Coagulation tests were rechecked if they were abnormal and following treatment with blood products.

SNAPPE-II

The SNAPPE-II for each neonate was determined using the physiological and laboratory data abstracted from the medical record. The following variables were used to determine the score: lowest mean blood pressure, lowest core temperature, partial pressure of arterial oxygen (PaO₂), fraction of inspired oxygen (FiO₂), lowest serum pH, presence of multiple-seizure activity, urine output, birth weight, being small-for-gestational age, and the 5-min Apgar score. SNAPPE-II was calculated for each infant by adding the composite scores of the physiologic and laboratory parameters (Supplementary Table 1, online) [13].

Diagnosis of intraventricular hemorrhage

The diagnosis and grading of IVH were based on the results of cranial ultrasounds obtained using a bedside ultrasound machine (Philips iU22, C8-5 probe) as part of routine clinical care and read by trained radiologists. IVH was graded using Papile’s grading system [21]: Grade 1 = blood in the subependymal germinal matrix; Grade 2 = blood within the ventricle, but without ventricular dilation; Grade 3 = blood in the ventricle with ventricular dilation; and Grade 4 = blood in brain parenchyma. When IVH was bilateral and varied in grade between hemispheres, the worst grade of hemorrhage was used for classification. Similarly, when infants had more than one ultrasound examination, the one demonstrating the highest grade of IVH was used for classification. Grades 3 and 4 IVH were grouped together as severe IVH. Infants with grades 1 or 2 IVH and those with no IVH were grouped together as no-mild IVH group.

Statistical methods

Continuous baseline characteristics are described as mean and standard deviation, and categorical
Variables as frequency and percentage. Median and range were used to express values that were not normally distributed. Means were compared between severe IVH (Grades 3 and 4) versus no-mild IVH (Grades 0, 1, and 2) using two-sample t-tests, and the medians were compared using Wilcoxon two-sample tests. Categorical variables between groups were compared using Pearson’s chi-square or Fisher’s exact test.

To assess whether demographic and clinical measures provide complementary information and can be combined for better prediction of IVH, we considered a multiple logistic regression model. This model predicts the odds of developing severe IVH versus no-mild IVH as a weighted linear combination of one or more predictors. As potential predictors, we considered birth weight, gestational age, sex, race, type of delivery, maternal age, 5 min Apgar score, SNAPPE-II, platelet count (10^9/mL), and coagulation parameters (PT, INR, PTT, and fibrinogen). Predictors in the model were determined by a stepwise (forward-backward) selection approach using a coefficient of p values < .05 as the inclusion criteria. Predictors that are not statistically significant (i.e. that do not improve predictions significantly given the other measures considered) were not included.

All analyses were conducted using SAS (version 9.3, Institute, Cary, NC, USA) and R (Version 3.2, R Foundation for Statistical Computing, Vienna, Austria), p < .05 was considered statistically significant.

**Results**

A total of 118 infants born between 2008 and 2013 were within the target gestational age range of <29 weeks. Sixteen neonates were excluded due to nonavailability of the coagulation profile, and one infant died before a cranial ultrasound could be obtained. Thus, the final study population consisted of 101 infants. Table 1 shows maternal and neonatal demographics. Thirty-two infants (31.7%) were born at 23 0/7–24 6/7 week, 35 (34.7%) at 25 0/7–26 6/7 week, and 34 (33.6%) at 27 0/7–28 6/7 weeks. The mean (SD) gestational age was 25.6 (1.8) weeks. Birth weight ranged from 380–1389 g. The infant population was 54% African American and 29% Hispanic, with an approximately equal number of males (51.5%) and females (48.5%). All infants received vitamin K per unit protocol. Delayed cord clamping was not part of neonatal care of preterm infants <29 weeks in our institution at the time of the study. All infants had at least one cranial ultrasound within the first week of birth and 82% (83/101) had a second cranial ultrasound between 7 and 37 days of life. Among the 18 who did not get the second ultrasound, 15 had a normal first-week ultrasound, 1 had grade 1 hemorrhage on the right side and 2 infants died before the second week. Forty-three (43%) infants had a diagnosis of IVH within the first week; 28 (28%) were diagnosed with grades 1 or 2 (mild IVH), and 15 (15%) with grades 3 or 4 (severe IVH). No new hemorrhages were discovered on the second head ultrasound in any of the infants.

The no-mild IVH and severe IVH groups differed in mean birth weight (835 versus 671 g, p = .008), mean gestational age (25.8 versus 24.5 wks, p = .006) and race (African American, 50 versus 80%, p = .031). Median SNAPPE-II was lower in the no-mild IVH group when compared with severe IVH group (30 versus 56, p = .001, Figure 1). There were no differences in the SNAPPE-II between the no IVH and mild IVH groups (Figure 1). Among the coagulation parameters, median

| Table 1. Maternal and neonatal characteristics. |
|-----------------------------------------------|
| Total (n = 101) | No-Mild IVH (n = 86) | Severe IVH (n = 15) | p-value |
|-----------------|----------------------|---------------------|---------|
| Birth weight (Mean, SD, g) | 811 (224) | 835 (226) | 671 (157) | .008 |
| Gestational age (Mean, SD, weeks) | 25.6 (1.8) | 25.8 (1.7) | 24.5 (1.6) | .006 |
| Sex, male, n (%) | 52 (51) | 42 (49) | 10 (67) | .202 |
| Race, black, n (%) | 55 (54) | 43 (50) | 12 (80) | .031 |
| Delivery, C-section, n (%) | 65 (64) | 56 (65) | 9 (60) | .703 |
| Mortality, n (%) | 8 (8) | 6 (7) | 2 (13) | .339 |
| Maternal age (Mean, SD, yrs) | 26.5 (6.7) | 26.8 (6.9) | 24.6 (5.3) | .246 |
| APGAR < 5 (5 min) | 7 (7%) | 4 (5%) | 3 (20%) | .065 |
| Antenatal steroids, n (%) | 65 (74%) | 57 (77%) | 8 (57%) | .123 |
| SNAPPE-II score (Median) | 34.8 (21.4) | 30 (0–101) | 56 (10–76) | .001 |
| Platelets, 10^6/mL (Median) | 200 (66) | 199 (49–376) | 161 (51–324) | .034 |
| Fibrinogen, mg/dL (Median) | 166 (106) | 152 (42–759) | 140 (64–316) | .661 |
| Prothrombin Time, sec (Median) | 21.4 (9.5) | 18.6 (13.4–86.6) | 25.6 (13.9–40.5) | .004 |
| INR (Median) | 1.9 (0.8) | 1.7 (1.2–7.5) | 2.3 (1.3–6.0) | .004 |
| Partial Thromboplastin Time, sec (Median) | 70.3 (19.7) | 65.4 (24.3–119.7) | 75.9 (48.4–136) | .149 |
| Thrombin Time, sec (Median) | 27.3 (8.2) | 25.5 (12.9–74.4) | 27.7 (16.5–41.5) | .342 |

IVH: Intraventricular hemorrhage, diagnosed within first week after birth; SNAPPE-II: Score for Neonatal Acute Physiology – Perinatal Extension II. **Missing 13 values (n = 88).” Fisher’s exact test. Bold represent significant p values.
PT (18.6 s versus 25.6 s, \( p = .004 \)), INR (1.7 versus 2.3, \( p = .004 \)) and platelet count (199,000/ml versus 161,000/ml, \( p = .03 \)) were different between the no-mild IVH and severe IVH groups. There were no differences with respect to maternal age, mode of delivery and mortality between the no-mild IVH and severe IVH groups (Table 1).

The stepwise logistic regression selected only SNAPPE-II as a predictor for severe IVH. All other demographic and clinical variables had an insignificant coefficient (\( p \)-values > 0.05) when included in a bivariate logistic model with SNAPPE-II. Conversely, SNAPPE-II remained significant (\( p \)-values < 0.05) for all bivariate models considered. The area under the receiver operating characteristic curve (AUC) for the model with only SNAPPE-II was 0.78 (95% CI: 0.63, 0.90). The full logistic model for log-odds of developing severe IVH is 

\[
/C0 + 0.045/C2 \times \text{SNAPPE-II};
\]

thus, the model implies a 5% chance of severe IVH for a SNAPPE-II of 14, a 25% chance of severe IVH for a SNAPPE-II of 55, and a 50% chance of severe IVH for a SNAPPE-II of 79. A threshold of 55 on the SNAPPE-II yielded a sensitivity of 60% (9/15), a specificity of 91% (78/86), a positive predictive value (PPV) of 53% (9/17) and a negative predictive value (NPV) of 93% (78/84). None of the coagulation parameters predicted the risk of severe IVH beyond that predicted by SNAPPE-II. Based on the predictive model, for each unit increase in SNAPPE-II, the log-odds of severe IVH increased by 0.045 (95% CI: [0.017, 0.073]; \( p = .002 \)).

**Discussion**

IVH continues to be a major risk factor for adverse long-term neurological sequelae in preterm infant <29 weeks. Fifteen percent (15%) of the infants in our study developed severe IVH, which is similar as the incidence reported in a previous study [22]. The present study demonstrates that SNAPPE-II at 12 h is the best predictor of severe IVH in this population. The study confirms the previous observations that lower birth weight and gestational age, African American race, and abnormal coagulation parameters are associated with severe IVH [23–25]. However, SNAPPE-II remained as a single independent predictor of severe IVH when compared with these clinical and laboratory variables.

Models that predict the risk of severe IVH in an individual infant have been developed and validated in previous studies [26,27]. The AUC for the predictive model with only SNAPPE-II in our study (0.78) is comparable to the AUC of 0.79 in the Luque et al. study [26] and 0.85 in the Singh et al. study [27]. However, both these studies used clinical variables within 6 h of birth for designing their model. Risk assessment within 6 h of birth is useful for deciding prophylactic interventions (e.g., indomethacin administration) for prevention of IVH. The Luque et al. study included respiratory illness (respiratory distress syndrome and mechanical ventilation) in the model, but not markers of hemodynamic instability (e.g., mean blood pressure, metabolic acidosis and urine output) which has been implicated in the pathogenesis of IVH [28]. Furthermore, clinical instability data collected within 12 h of birth has the potential to be of low quality [13]. To our knowledge, ours is the first study to assess the usefulness of SNAPPE-II for predicting the risk of severe IVH in a preterm infant <29 weeks. A prior study demonstrated that an arbitrarily chosen SNAPPE-II >45 increases the odds of IVH (grade not mentioned) by 50% in the <28-week gestation preterm population [14]. The present study demonstrates that a SNAPPE-II of 55 implies a 25% chance of severe IVH and a SNAPPE-II of 79, a 50% chance of severe IVH. Such information is useful for counseling parents; however, needs validation through larger prospectively conducted studies.

Prior studies have reported an association between severe IVH and longer INR and PT at birth [23,25,29], a finding also seen in the present study. In addition, there was an association between low platelet count and severe IVH. However, abnormal coagulation parameters, as well as low platelet count had an insignificant coefficient (\( p \)-values > 0.05) when included in a
bivariate logistic model with SNAPPE-II, suggesting that they do not provide additional predictability beyond that provided by SNAPPE-II. This could mean that routine coagulation screening may not be necessary for this population. However, whether coagulation parameters should be monitored and abnormal values treated using blood products in those with high SNAPPE-II remains unclear. Similarly, whether transfusion of blood products led to severe IVH in infants with higher SNAPPE-II is difficult to establish in the present study, although such transfusions were also administered to correct abnormal coagulation parameters in the no-mild IVH group.

This study has limitations. Despite our attempts to include all clinical variables that have been implicated in severe IVH, it is possible that other relevant clinical variables may have been excluded. The relatively small number of infants with severe IVH and the retrospective nature of the study are additional limitations.

In conclusion, our study shows that the severity of illness based on SNAPPE-II at 12 h after birth is a good predictor of severe IVH in a <29 weeks preterm infant.

Acknowledgments

We thank Minneapolis Medical Research Foundation (MMRF) and HCMC NICU Staff for their support. We thank Ms. Qi Wang, from the Department of Biostatistics, University of Minnesota for providing statistical support.

Disclosure statement

No potential conflict of interest was reported by the authors.

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