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ORIGINAL ARTICLE

A risk prediction model for severe intraventricular hemorrhage in very low birth weight infants and the effect of prophylactic indomethacin

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OBJECTIVE: Develop a risk prediction model for severe intraventricular hemorrhage (IVH) in very low birth weight infants (VLBWI).
STUDY DESIGN: Prospectively collected data of infants with birth weight 500 to 1249 g born between 2001 and 2010 in centers from the Neocosur Network were used. Forward stepwise logistic regression model was employed. The model was tested in the 2011 cohort and then applied to the population of VLBWI that received prophylactic indomethacin to analyze its effect in the risk of severe IVH.
RESULT: Data from 6538 VLBWI were analyzed. The area under ROC curve for the model was 0.79 and 0.76 when tested in the 2011 cohort. The prophylactic indomethacin group had lower incidence of severe IVH, especially in the highest-risk groups.
CONCLUSION: A model for early severe IVH prediction was developed and tested in our population. Prophylactic indomethacin was associated with a lower risk-adjusted incidence of severe IVH.

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Keywords: intracranial hemorrhage; preterm infant; risk score

INTRODUCTION

Severe intraventricular hemorrhage (IVH) in the premature infant is an acquired lesion with a potentially enormous impact on morbidity, mortality and long-term neurodevelopmental outcome.[1] Over recent decades, improvements in obstetrical and neonatal care have contributed to a significant decline in mortality and overall incidence of IVH in premature infants,[2–4] ranging from 50% in the late 1970s to the current 15 to 25%.[1,5–7] However, the improvement in survival rates of very low birth weight infants (VLBWI)[6,8] has led to an increase in the population of newborns susceptible to develop IVH. Another point for concern is that the incidence of grade 3 to 4 IVH has not changed over the last decade,[9] with rates reported by the NICHD neonatal network of approximately 16% in VLBWI, accounting for 50% of the overall incidence of IVH.[10] Furthermore, more than three quarters of these infants develop mental retardation or cerebral palsy and 45 to 86% are reported to suffer major cognitive handicaps.[9] Therefore, to decrease the incidence of severe IVH and thus potentially improve neurodevelopmental outcome in the preterm population, successful preventive therapies are required. Targeting the most vulnerable population for severe IVH may contribute in the evaluation of such therapies.

The highest risk period for developing IVH is independent of gestational age (GA) and is more common within the first 24 h after birth. Hemorrhages can progress over 48 h or more; thereby, at the end of the first postnatal week, 90% of IVH can be detected at their full extent.[9] Owing to perinatal onset of IVH, prevention strategies should be addressed by antenatal, intrapartum and early postnatal approaches. At the same time, the IVH's tendency to progress and the delay in the appearance of some of its complications such as periventricular hemorrhagic infarction and posthemorrhagic hydrocephalus suggest there could be a therapeutic window during which preventive interventions can be effective.[1]

Several pharmacologic prevention strategies have been studied. Among antenatal pharmacologic interventions, corticosteroids are currently the only strategy that has consistently been associated with a reduction in both the incidence of IVH and overall mortality rates.[11] Another appealing antenatal treatment is magnesium sulfate, which has been associated with lower risks of cerebral palsy, but with no apparent effect in IVH incidence.[1,12] Antenatal phenobarbital and vitamin K have not been proved to be beneficial for the prevention of IVH.[13] Several postnatal pharmacologic agents have been proposed for IVH prevention; among them prophylactic indomethacin has shown a significant decrease in the overall incidence and severity of IVH.[14] However, follow-up studies showed no beneficial effect on the incidence of cerebral palsy and only modest effects on cognition.[15–17] Nevertheless, these prevention strategies also have potential adverse effects, which reinforces the importance of carefully selecting those infants that are at greatest risk of developing IVH and may benefit the most from these interventions.

The main purpose of our study was to develop an early-risk prediction model for severe IVH (grades III and IV) in VLBWI with birth weight (BW) between 500 and 1249 g. As a secondary objective the risk model was applied in the subpopulation of

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VLBWI that had received prophylactic indomethacin to analyze its association with the incidence of severe IVH.

METHODS

Our study used information from the Neocosur Neonatal Network database, which includes 23 neonatal intensive care units from six South American countries: Argentina, Brazil, Chile, Paraguay, Peru and Uruguay. All network centers are tertiary care and university affiliated. This network provides a continuous database that prospectively gathers information from all inborn VLBWI (BW from 500 to 1500 g) from the participating centers. Patient identity is kept confidential. This study was approved by the local ethics committee.

We included data of all inborn infants with BW between 500 and 1249 g admitted from 1 January 2001 to 31 December 2010. Exclusion criteria included infants who received prophylactic indomethacin, who died in the delivery room or who had major malformations. The diagnosis of IVH was made by cranial ultrasonogram or by autopsy and was classified according to Papile and Bursten,[18] considering as severe grades 3 to 4. Demographic and clinical information and outcome data were prospectively and systematically collected at the Neocosur Network centers using predefined diagnostic criteria and online data entries.

Continuous variables are shown as mean and standard deviation, whereas categorical variables are shown as number of cases and percentages. To compare populations with and without severe IVH, Student's *t*-test was used to compare means for independent samples and chi-square test to compare proportions. All statistical analyses were done using standard statistical software (SPSS 19 program).

Multivariable stepwise logistic regression modeling was used to select those variables present at birth that were significantly associated with severe IVH risk. Variables included in the analysis were: gender, GA, BW, birth length, intrauterine growth retardation, antenatal corticosteroids (at least one dose), cesarean section, 1-min Apgar, 5-min Apgar, delivery room intubation, respiratory distress syndrome, mechanical ventilation and premature rupture of membranes. A significance level of 5% was used to include each variable in the model. Once the final model was created, the area under ROC curve (AUC) was then calculated.

Table 1. Patient characteristics and outcomes of all infants included in the study, and of those with and without severe IVH

Demographics and neonatal outcomes	*Overall*	*Patients without severe IVH*	*Patients with severe IVH*	P-*value*
N, %	6538	4890 (85.3%)	857 (14.7%)	
Birth weight, mean ± s.d.	953 ± 201	986 ± 190	855 ± 189	<0.001
Gestational age, mean ± s.d.	28.1 ± 2.6	28.6 ± 2.5	26.7 ± 2.2	<0.001
Male gender, %	50.3	48.4	58.1	<0.001
Cesarean section, %	70.3	75.1	57.1	<0.001
No antenatal steroids, %	23.8	18.5	33.8	<0.001
Incomplete antenatal steriods, %	19.1	18.6	22.1	<0.001
Complete antenatal steroids, %	57.2	62.9	44.2	<0.001
1-min Apgar (median; 25–75th)	6 (4–8)	7 (5–8)	4 (3–7)	<0.001
5-min Apgar (median; 25–75th)	8 (7–9)	8 (7–9)	7 (6–8)	<0.001
Respiratory distress syndrome, %	81.2	78	95.4	<0.001
Mechanical ventilation, %	75.9	71.2	97.2	<0.001

Abbreviation: IVH, intraventricular hemorrhage.
Birth weight 500–1249 g (2001–2010).

Consecutively, the model was tested over a more recent population of VLBWI (BW between 500 and 1249 g) born between 1 January 2011 and 31 December 2011. The Hosmer–Lemeshow method of calibration was used. The AUC was calculated and compared with the value obtained from the final model.

As the Neocosur Network includes various neonatal intensive care units that differ greatly in terms of resources, population served and outcomes, we additionally tested the model individually in each center to evaluate if it maintains its predictive properties. The AUC for each center was also calculated and compared with the final model.

A cutoff value was calculated at the point where the model reached its higher sensitivity and specificity, above which the probability of developing IVH is statistically greater and is considered as a 'positive' test. Likelihood ratios were then calculated and applied to a Fagan nomogram, to illustrate how the predictive model changed post-test probability when it was used.

As an adjoining analysis, the risk predictive model was applied to the population of VLBWI that received prophylactic indomethacin, to compare the percentage of observed severe IVH by risk quintiles between both populations of VLBWI: those who received prophylactic indomethacin versus those who did not. For this analysis we studied all inborn infants with BW between 500 and 1249 g admitted from 1 January 2001 to 31 December 2010 who received prophylactic indomethacin, excluding those who died in the delivery room or had major malformations.

RESULTS

Data from 6538 infants with BW 500 to 1249 g born between 2001 and 2010 who met the inclusion criteria were analyzed. Mean GA was 28.1 ± 2.6 weeks (s.d.) and mean BW was 953 ± 201 g (s.d.). The incidence of severe IVH for the total group was 14.9% (range 5 to 25.4%), with a missing data rate of 12.1% ($n = 791$ infants) for this outcome, including 406 infants that died in the delivery room. Other 986 infants were excluded in the development of the model because they had received prophylactic indomethacin and 14 because they presented major congenital malformations. The biodemographic characteristics and outcomes for the overall population and for patients with and without severe IVH are presented in Table 1. All variables studied had a *P*-value <0.001.

Table 2 shows the variables included in the final predictive model selected by a multivariable stepwise logistic regression model, with their respective odds ratio, AUC and percentage increase in AUC. The variables excluded because they provided no improvement in the model were: birth length, 5-min Apgar, intrauterine growth retardation, delivery room intubation and premature rupture of membranes. GA was the major contributor to the model, followed by mechanical ventilation, antenatal steroids, 1-min Apgar score, BW, cesarean section, male gender and respiratory distress syndrome. Mechanical ventilation was the variable associated with a major increase in risk of severe IVH, with an odds ratio of 4.59, whereas cesarean section was the variable associated with a major decrease in risk of severe IVH, with an odds ratio of 0.65. The AUC for the overall model was 0.787.

To test the model, data of 944 infants born during 2011 that met the same inclusion criteria were analyzed. Figure 1 shows and compares ROC curves for the 2011 cohort and for the final model, both being very similar. The AUC for the 2011 cohort was 0.764, slightly differing from the AUC of the model. When testing the model by center, ROC curves for each center were very similar, with AUC ranging from 0.708 to 0.890.

The cutoff point of the model where it reached the highest sensitivity and specificity was a probability ⩾17%. This means that when the model is applied and a probability of 17% or greater is obtained, the chance of developing severe IVH is statistically significant, so it is considered as a positive test. The sensitivity of the model was 71.9% and the specificity 71.7%. Positive likelihood ratio was 2.5 and negative likelihood ratio was 0.39. Thus, considering the pre-test probability as the prevalence of severe IVH in this population (14.9%), the post-test probability increases to almost 30% when there is a positive test (probability ⩾17%)

Table 2. Variables selected by multivariable stepwise logistic regression model

Variable	*Coefficient*	*s.e.*	*OR*	*95% CI*	*AUC*	*% Increase in AUC*
Gestational age (per week)	−0.134	0.025	0.875	0.832–0.919	0.717 ± 0.009	
Mechanical ventilation	1.524	0.230	4.591	2.926–7.202	0.746 ± 0.008	2.9
With antenatal steroids[a]	−0.684	0.087	0.504	0.425–0.598	0.760 ± 0.008	1.4
1-min Apgar	−0.094	0.019	0.888	0.859–0.918	0.771 ± 0.008	1.1
Birth weight (per 100 g)	−0.125	0.025	0.882	0.840–0.927	0.775 ± 0.008	0.4
Cesarean section	−0.422	0.087	0.655	0.553–0.777	0.782 ± 0.008	0.7
Male gender	0.339	0.082	1.404	1.196–1.649	0.785 ± 0.008	0.3
Respiratory distress syndrome	0.514	0.182	1.672	1.172–2.387	0.787 ± 0.008	0.2

Abbreviations: AUC, area under ROC curve; CI, confidence interval; OR, odds ratio.
[a]At least one dose.

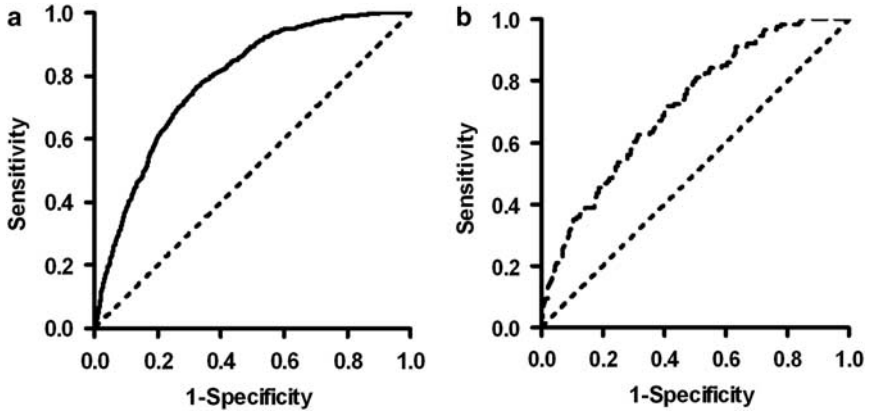

Figure 1. ROC curves for the final model (**a**) and the 2011 cohort testing (**b**).

and decreases to almost 5% when there is a negative test (probability ⩽17%).

Figure 2 shows the observed percentage of severe IVH by risk quintiles for the populations with and without prophylactic indomethacin. The prophylactic indomethacin group had a lower incidence of severe IVH. This effect was statistically significant (*P*-value <0.05) in the higher-risk groups (mainly quintiles 4 and 5), and not significant in quintiles 1 and 3.

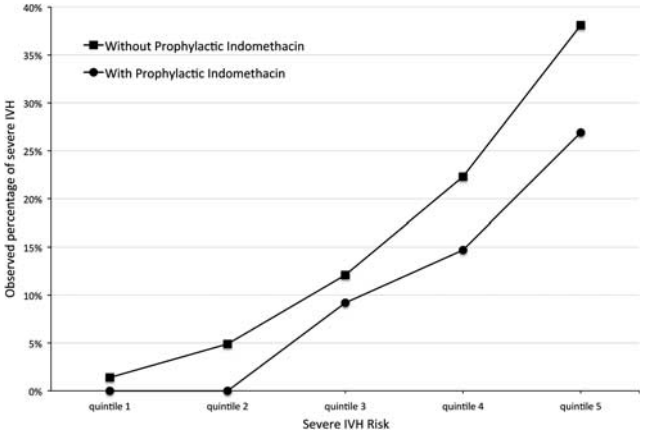

Figure 2. Observed percentage of severe IVH by risk quintiles for the populations with and without prophylactic indomethacin.

DISCUSSION

We developed an early-risk prediction model for severe IVH (grades III and IV) in VLBWI. The web-based version of this tool is available at https://www.neocosur.org.

Ever since a diagnostic classification of IVH was published by Papile and Bursten,[18] several studies have identified numerous perinatal/obstetric and neonatal risk factors associated with this outcome. These factors include the ones selected in our study, plus others such as maternal chorioamnionitis/infection/inflammation, antenatal maternal hemorrhage, neonatal transport, early sepsis, acidosis, hypotension, hypoxemia, hypercapnia, pneumothorax, transfusions, treatment with vasopressors, seizures and specific gene mutations.[19–26,27] There is sufficient evidence to suggest that the causal pathway leading to IVH begins in the antenatal, intrapartum or early postnatal period, which explains why IVH is most commonly encountered within the first 24 h after birth.[28–30] Accordingly, major risk factors associated with IVH may be identified early after birth. Therefore, despite the existence of this large list of risk factors for IVH mentioned above, we could only select those factors available in the network database that were present early after birth. Moreover, for many of these risk factors a clear causal relationship has not been established, some of them being probably more a consequence than a cause associated to the IVH pathway.

In the present study eight variables remained highly significant when entered simultaneously into the multivariate regression analysis. We found that GA was the major predictor of severe IVH, which agrees with previous studies.[25,31–34] Mechanical ventilation was the categorical variable associated with a major increase in risk of severe IVH. This finding, associated with a lower role of respiratory distress syndrome as a predictor of severe IVH,

suggests that severe respiratory distress leading to intubation is ultimately a better predictor for severe IVH. Antenatal steroids and cesarean section were the variables associated with a major decrease in the risk of severe IVH. The protective role of antenatal corticosteroids is well recognized.[11] Our analysis confirms their importance, with even partial treatment having a beneficial effect in reduction of severe grades of IVH. A number of studies have examined whether delivery practices affect the incidence of IVH. Although often contradictory, these results suggest the possibility that active labor and vaginal delivery may be a risk factor for developing early-onset IVH.[35] Cesarean section has been suggested by some investigators as being beneficial for avoiding the increased cerebral venous pressure during vaginal labor and for preventing IVH,[32,36–40] whereas others could not demonstrate such an association.[23,41] The present study provides evidence that delivery of the very immature infant by cesarean section may reduce IVH. The other variables included in the model, such as male sex, lower 1-min Apgar score and lower BW, also showed maintained significance as risk factors, in agreement with other reports.[25,34,42–45]

The model AUC is reasonably good (0.787) and when tested in the 2011 cohort remained almost unchanged (0.764), confirming the temporal stability of the model. Additionally, there was no great variability in AUC among centers. Furthermore, when using a cutoff point and calculating likelihood ratios we can see that the model gives us a closer approximation for severe IVH risk, which reinforces its usefulness as a tool for targeting possible preventive strategies in a selected group of patients.

As mentioned above, several studies have reported risk factors associated with IVH, but there are only a few that have attempted to develop risk prediction models for this outcome. Van de Bor *et al.*[31] were the first to report the predictive value of several maternal, prenatal and postnatal factors for the development of neonatal IVH grades I to IV, finding that GA appeared to be the strongest predictive factor for both incidence and severity of IVH, which is consistent with our findings. Heuchan *et al.*[25] developed a predictive model for major IVH and performed risk-adjusted comparisons among neonatal intensive care units of the Australian and New Zealand Neonatal Network. The final model included five antenatal and early-neonatal factors: GA, antenatal corticosteroids, transfer after birth, 1-min Apgar score <4 and gender. Four of these variables are coincident with our model. More recently, Vogtmann *et al.*[32] developed a risk prediction model for IVH (all grades) with the same purpose as Heuchan *et al.* In addition to GA, the variables most closely related to IVH risk were a low 1-min Apgar score (<6), followed by early infection (<3 days). In agreement with our study, they also found a protective effect of cesarean section, but it was not included in the final model. In contrast to our study and other reports,[25,42,44–45] they did not find a higher risk of IVH for male gender. Although these studies are methodologically very similar to ours, their main purpose was to develop a predictive model to allow risk adjustment and compare IVH rates among different neonatal intensive care units. In contrast, the objective of our study was to develop a risk score that can be individually used for severe IVH prediction in VLBWI.

Other studies analyze the utility of neonatal illness severity scores validated for mortality risk prediction, such as the CRIB[33] and SNAP-II,[34] in predicting severe IVH. Both scores were useful as predictors of severe IVH. Furthermore, the addition of traditional risk factors such as GA and perinatal risks to SNAP-II increases the predictive performance and discriminative power of the models for prediction of severe IVH.[34]

Our results also show that prophylactic indomethacin was associated with a lower incidence of severe IVH in this VLBWI population. This is consistent with several trials where treatment with prophylactic indomethacin has shown to decrease the incidence and severity of IVH.[14–17,46–48] Furthermore, the present study adds that after adjusting for risk, the beneficial effect of indomethacin is more prominent and significantly greater in the two highest risk quintiles. This constitutes an interesting finding that allows us to speculate that probably the effect of prophylactic indomethacin in long-term neurological outcomes becomes more significant when the highest-risk population of VLBWI is studied. Thus, more studies directed to the most vulnerable population for severe IVH should be addressed to evaluate its long-term effects that till now persist as controversial.

This study has several limitations. The analysis was limited to variables included in our network database, perhaps excluding other potentially important factors to be considered. However, many of these factors present late after birth and therefore do not apply to the study purpose. The other limitation is a high percentage of missing data, mainly due to early death, before an ultrasound and without autopsy. Finally, the results may apply to our population but not necessarily to others.

We conclude that an early-prediction model with factors present in the first few hours of life may be useful in a clinical setting, allowing the selection of premature infants at a greatest risk for severe IVH. This may improve allocation of resources to the most vulnerable population and targeting for potential preventive therapies. Prophylactic indomethacin is associated with a reduction of severe IVH in the highest-risk infants, but not in the ones at lower risk.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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APPENDIX

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