Prevalence, Risk Factors and Intra-Hospital Outcomes Relating to Peri-Intraventricular Hemorrhage in Premature Newborns of Gestational Age Less than 34 Weeks

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Abstract

Peri-intraventricular hemorrhage is one of the main causes of neurological impairment in premature newborns. To control their risk factors is necessary in view of the increasing survival of extreme preterm infants. Objective: To evaluate the prevalence of peri-intraventricular hemorrhage in premature newborns, identify the risk factors and observe the frequencies of intra-hospital outcomes of interests. Methods: This study was done in Brazil. This was an observational, analytical longitudinal and prospective study. The subjects included were newborns of gestational age less than 34 weeks who were admitted to two public hospitals between May and November 2015. To assess possible associated factors, obstetric, perinatal and neonatal data were analyzed (chorioamnionitis, antenatal corticosteroids, gestational age, newborn weight, Apgar score at 1 and 5 minutes, resuscitation in the delivery room, surfactant in the delivery room, newborn transferred from another hospital, respiratory distress syndrome: RDS, sepsis, umbilical vein catheterization, assisted ventilation, exogenous surfactant in the Neonatal ICU, use of sodium bicarbonate, inotropic agents, adrenaline, volume expanders and blood products). The hospital outcomes studied were assisted ventilation time, hospital stay and death. The data analysis was performed by chi-square test or Fisher's test, with a significance level of 5%. Results: Out of 156 newborns, 46 (29.9%) presented peri-intraventricular hemorrhage and 28.2% of these had a severe form of the disease. There were significant associations ($p < 0.05$) with the

following risk factors: gestational age, birth weight, low Apgar score, delivery room resuscitation, RDS, surfactant use, sepsis, packed red blood cell transfusion, mechanical ventilation and umbilical vein catheterization. The newborns with peri-intraventricular hemorrhage presented longer times on assisted ventilation, longer hospital stays and higher risk of death. Conclusion: The prevalence of peri-intraventricular hemorrhage was high in the population studied, especially the severe form. Perinatal and neonatal risk factors were associated with a higher risk of developing the disease and the outcomes studied were more evident in these newborns.

Keywords

Premature Newborn, Peri-Intraventricular Hemorrhage, Risk Factors, Transfontanelle Ultrasonography

1. Introduction

With the advances in perinatal medicine and neonatal intensive care that have been achieved, there has been a significant increase in survival among premature newborns. However, it has been observed that the incidence of neurological impairment among these newborns continues to be high, and peri-intraventricular hemorrhage is one of its main causes [1] [2] [3] [4]. Peri-intraventricular hemorrhage typically begins in the subependymal germinal matrix, which is a richly vascularized region in the developing brain, but with limited capacity for self-regulation of the cerebral blood flow [5].

At the beginning of the 1980s, the incidence of peri-intraventricular hemorrhage was 50% [5]. In a recent study, morbidity among premature newborns was evaluated and, in comparing the frequency of peri-intraventricular hemorrhage between Taiwan (China), Canada, Japan and the United States, it was observed that severe peri-intraventricular hemorrhage was diagnosed in 14.0%, 18.0%, 10.0% and 19.0% of the cases, respectively [6]. In Brazil, data from 20 university hospitals that were presented in the 2014 annual report of the Brazilian Network for Neonatal Research showed that the incidence of peri-intraventricular hemorrhage among premature newborns weighing less than 1500 g was 30%, and that this condition was severe in 9% of these cases [7].

The first classification system for peri-intraventricular hemorrhage was developed by Papile *et al.* (1978), using computed tomography [8]. This system was applied to cerebral ultrasonography and was found to have high sensitivity and specificity rates in relation to detecting peri-intraventricular hemorrhage. It has become widely used, and this continues today [9] [10].

The frequency of occurrence and severity of peri-intraventricular hemorrhage becomes greater when the gestational age and birth weight are lower [11] [12] [13]. However, several other prenatal factors (rupture of membranes, presence of chorioamnionitis or nonuse of antenatal corticoids), perinatal factors (low Ap-

gar index, use of reanimation or use of surfactant) and postnatal factors (respiratory distress syndrome, sepsis, volume expanders, mechanical ventilation and use of drugs like inotropes and sodium bicarbonate) have been correlated with higher risk of developing the disease [1] [2] [14] [15].

Knowledge of the prevalence of peri-intraventricular hemorrhage among premature newborns and of the risk factors involved in each neonatal intensive care unit is necessary so that preventive measures can be brought in. Studying this condition is of great interest because of its association with increased neonatal morbidity and mortality, longer hospital stay and higher risk of development of cognitive and motor deficits.

Thus, the aim of the present study was to evaluate the prevalence of peri-intraventricular hemorrhage among premature newborns, identify the risk factors and observe the frequencies of intra-hospital outcomes of interest (duration of assisted ventilation, length of hospital stay and death).

2. Material and Methods

This study was approved by the Research Ethics Committee of the Cesmac University Center, under the number 1.064.913. The population was composed of premature newborns of gestational age between 25 weeks and 33 weeks and 6 days who were hospitalized in the neonatal intensive care units of two tertiary-level public university hospitals in the state of Alagoas between May and November 2015. Newborns with congenital malformations, those for whom no ultrasonography examination had been performed up to the fourth day of life and those who were transferred to other hospital services providing lower-complexity cases before the tenth day of life were excluded. The newborns who were transferred after the tenth day underwent the ultrasonography examinations of the protocol of the present study, and their outcomes of interest were followed up until the time of discharge from hospital. These newborns remained in the study group.

An echograph with 5 to 10 MHz transducers (GE LOGIC P6) was used. For documentation purposes, the examinations were recorded on CDs for subsequent analysis. The images were obtained via the anterior and posterior fontanelles.

The population of this study underwent serial cerebral ultrasonography, within the first four days of life, on the 10th and 28th days and at discharge from hospital.

The newborns were stratified into three gestational age groups that took into consideration the level of development inherent to each stage: 25 weeks to 27 weeks and 6 days; 28 weeks to 30 weeks and 6 days; and 31 weeks to 33 weeks and 6 days [16].

Among the newborns with a diagnosis of peri-intraventricular hemorrhage, the widely used classification system proposed by Papile *et al.* (1978) was applied, namely: grade I—subependymal hemorrhage; grade II—intraventricular

hemorrhage without dilatation; grade III—intraventricular hemorrhage with dilatation; and grade IV—presence of an echogenic area in the periventricular tissue with or without intraventricular hemorrhage. Hemorrhages of grades I and II are classified as mild; and those of grades III and IV as severe [8].

The data relating to the dependent variable (peri-intraventricular hemorrhage) were obtained through transfontanelle ultrasonography performed in the neonatal unit and were stored on a CD and catalogued using a specific form for this purpose. The data relating to the independent variables were gathered using data collection forms that contained questions relating to the pregnancy, birth and neonatal evolution until discharge from hospital. This information came from the medical records relating to both the mother and the newborn.

In the statistical analysis, the quantitative variables were presented in the form of means, standard deviations and minimums and maximums. The qualitative variables were presented in the form of frequency tables. In inferential statistical analyses, the presence of associations between the dependent variable and the independent variables was ascertained through the chi-square test or Fisher's exact test.

In all the analyses, the significance level was taken to be $p \leq 0.05$. The data were tabulated using Excel electronic spreadsheets (Microsoft Office) and statistical inferences were made through the application SPSS 20.0.

3. Results

Over the period of this study, *i.e.* from May to November 2015, 176 newborns of gestational ages less than 34 weeks were admitted to the two neonatal intensive care units investigated. Twenty newborns (11.4%) were excluded from the study: five because they died before the first ultrasonography examination could be performed; two because of malformation of the central nervous system; seven because no transfontanelle ultrasonography was performed; and six because they were transferred to hospitals providing care for lower-complexity cases before the tenth day of life. Among the 156 newborns who were eligible for inclusion, 46 (29.5%) presented peri-intraventricular hemorrhage. The distribution of peri-intraventricular hemorrhage cases according to severity is shown in **Table 1**.

It was observed that 28.2% of the peri-intraventricular hemorrhage cases were

Table 1. Distribution of the severity of peri-intraventricular hemorrhage among newborns of gestational age less than 34 weeks, according to the classification system of Papile *et al.* (1978).

Grade	N	Frequency
Grade I	23	50%
Grade II	10	21.8%
Grade III	9	19.5%
Grade IV	4	8.7%
TOTAL	46	100%

severe. Among all the 46 cases of peri-intraventricular hemorrhage, this condition was diagnosed as bilateral in 42 cases (91.3%) and unilateral in four cases (8.7%), among which three were left-side and one was right-side. The time at which peri-intraventricular hemorrhage was diagnosed was before the 4th day of life in 24 cases (52.3%), from the 4th to the 10th day of life in 20 cases (43.4%) and from the 10th to the 28th day of life in two cases (4.3%). In six cases (13.0%), there was progression of the peri-intraventricular hemorrhage after the initial diagnosis. Among these six cases, four had an initial diagnosis of peri-intraventricular hemorrhage grade I, of which two evolved to grade II and then one of these evolved to grade III. The other two these six cases initially presented peri-intraventricular hemorrhage grade II and evolved to grade III.

Among all the cases of peri-intraventricular hemorrhage that were studied, four (8.7%) evolved with post-hemorrhagic hydrocephaly. Of these, one case required ventriculoperitoneal shunt, while clinical and ultrasonographic follow-up was maintained for the other three cases. Among the four cases with post-hemorrhagic hydrocephaly, three presented peri-intraventricular hemorrhage grade III and one presented peri-intraventricular hemorrhage grade IV.

There were four newborns with presented peri-intraventricular hemorrhage grade IV, and one of them (25%) developed a porencephalic cyst, while the other three (75%) evolved to death (two on the 4th day of life and one on the 10th day of life).

Regarding the severity of peri-intraventricular hemorrhage in relation to gestational age, grade I was most frequently seen in the stratum from 31 weeks to 33 weeks and 6 days (70.7%); grade II in the stratum from 25 weeks to 27 weeks and 6 days (35.3%); grade III in the stratum from 28 weeks to 30 weeks and 6 days (25%); and grade IV in the stratum from 25 weeks to 27 weeks and 6 days (11.8%).

Table 2 shows the results relating to the presence of an association between the gestational and perinatal characteristics and the presence or absence of peri-intraventricular hemorrhage. It could be seen that peri-intraventricular hemorrhage became more frequent when the gestational age and birth weight were lower. Among newborns of gestational age < 28 weeks, the frequency of peri-intraventricular hemorrhage was 37%. Among newborns weighing < 1000 g, the frequency of peri-intraventricular hemorrhage was 43.5%. This condition occurred more frequently among newborns who had undergone reanimation in the delivery room (63%).

Data on the presence of associations between peri-intraventricular hemorrhage and pathological conditions among the newborns, and between peri-intraventricular hemorrhage and use of certain procedures, are shown in **Table 3**. It should be noted that all the newborns who evolved with peri-intraventricular hemorrhage had required some type of assisted ventilation before receiving their diagnosis. Peri-intraventricular hemorrhage occurred more frequently in newborns who received exogenous surfactant. However, there was no difference between the cases in which surfactant was applied in the delivery room and

Table 2. Associations of obstetric, perinatal and neonatal characteristics with the presence or absence of peri-intraventricular hemorrhage among newborns of gestational age less than 34 weeks.

Variable	Present (n = 46)		Absent (n = 110)		p-value ^a
	n	%	N	%	
Chorioamnionitis					
Yes	3	6.5	8	7.3	1.000
No	43	93.5	102	92.7	
Antenatal corticoids					
Yes	11	23.9	35	31.8	0.323
No	35	76.1	75	68.2	
Gestational age (weeks and days)					
25 w to 27 w 6 d	17	37.0	4	3.6	<0.001
28 w to 30 w 6 d	12	26.1	20	18.2	
31 w to 33 w 6 d	17	37.0	86	78.2	
Weight (g)					
500 - 999 g	20	43.5	7	6.4	<0.001
1000 - 1500 g	13	28.3	48	43.6	
>1500 g	13	28.3	55	50.0	
Apgar score in 1 st min					
0 - 3	11	23.9	7	6.4	0.003
4 - 6	17	37.0	32	29.1	
7 - 10	15	32.6	65	59.1	
No data	3	6.5	6	5.5	
Apgar score in 5 th min					
0 - 3	0	0	0	0	<0.001
4 - 6	13	28.3	4	3.6	
7 - 10	30	65.2	101	91.8	
No data	3	6.5	5	4.5	
Reanimation in delivery room					
Yes	29	63.0	29	26.4	<0.001
No	17	37.0	81	73.6	
Surfactant in delivery room					
Yes	13	28.3	17	15.5	0.064
No	33	71.7	93	84.5	
Transferred from another hospital					
Sim	17	37.0	34	30.9	0.463
Não	29	63.0	76	69.1	

^aChi-square test.

Table 3. Associations of neonatal characteristics (pathological conditions, procedures and clinical treatments) with the presence or absence of peri-intraventricular hemorrhage among newborns of gestational age less than 34 weeks.

Variable	Present (n = 46)		Absent (n = 110)		valor de p ^a
	n	%	n	%	
Respiratory distress syndrome					
Yes	41	89.1	43	39.1	<0.001
No	5	10.9	67	60.9	
Sepsis					
Yes	42	91.3	61	55.5	<0.001
No	4	8.7	49	44.5	
Catheterization of umbilical vein					
Yes	45	97.8	82	74.5	0.001
No	1	2.2	28	25.5	
Assisted ventilation					
Yes	46	100.0	100	90.9	---
No	0	0	9	8.2	
No supplementary O ₂	0	0	1	0.9	
Exogenous surfactant					
Yes	42	91.3	50	45.5	<0.001
No	4	8.7	60	54.5	
Sodium bicarbonate					
Yes	11	23.9	3	2.7	<0.001
No	35	76.1	107	97.3	
Inotropes					
Yes	16	34.8	6	5.5	<0.001
No	30	65.2	104	94.5	
Adrenalin					
Yes	9	19.6	1	0.9	<0.001
No	37	80.4	109	99.1	
Volume expanders					
Yes	19	41.3	14	12.7	<0.001
No	27	58.7	96	87.3	
Blood derivatives					
Yes	30	65.2	21	19.1	<0.001
No	16	34.8	89	80.9	

^aChi-square test.

those in which it was applied in the neonatal intensive care unit. It was observed that 97.8% of newborn submitted to umbilical vein catheterization had peri intraventricular, as well as the high frequency in those who used epinephrine and

blood products.

The association between intra-hospital outcomes and the presence or absence of peri-intraventricular hemorrhage is described in **Table 4**. It needs to be highlighted that 37% of the newborns who presented peri-intraventricular hemorrhage were in hospital for more than 60 days and that 10.9% of them were also receiving assisted ventilation. Among the newborns who evolved to death, 28.3% presented peri-intraventricular hemorrhage.

4. Discussion

This study demonstrated the prevalence of peri-intraventricular hemorrhage among premature newborns of gestational age less than 34 weeks, the risk factors associated with its development and the relationship with some intra-hospital outcomes (duration of assisted ventilation, length of hospital stay and frequency of occurrence of death), in two neonatal intensive care units in the state of Alagoas.

Over the period analyzed, from May to November 2015, the observed frequency of peri-intraventricular hemorrhage was 29.5%, of which 28.2% were classified as severe. These frequencies were higher than those of other countries and regions like Japan (10.0%), Taiwan (14.0%), Canada (18.0%) and the United States (19.0%) [6]. In Brazil, data from 20 university hospitals that were presented in the 2014 annual report of the Brazilian Network for Neonatal Research showed that the incidence of peri-intraventricular hemorrhage among premature

Table 4. Associations of intra-hospital outcomes with the presence or absence of peri-intraventricular hemorrhage among newborns of gestational age less than 34 weeks.

Variable	Present (n = 46)		Absent (n = 110)		p-value p ^a
	n	%	n	%	
Length of hospital stay					
0 to 10 days	10	21.7	24	21.8	<0.001
>10 to 28 days	0	0	42	38.2	
>28 to 60 days	19	41.3	40	36.4	
>60 days	17	37.0	4	3.6	
Death					
Yes	13	28.3	16	14.5	0.045
No	33	71.7	94	85.5	
Duration of assisted ventilation					
0 to 10 days	15	32.6	78	70.9	< 0.001
> 10 to 28 days	17	37.0	30	27.3	
> 28 to 60 days	9	19.6	2	1.8	
> 60 days	5	10.9	0	0	

^aChi-square test.

newborns weighing less than 1500 g was 30%, and that this condition was severe in 9% of these cases [7].

It is possible that the high prevalence of peri-intraventricular hemorrhage that was observed in the present study, especially among premature newborns of gestational age less than 28 weeks and with birth weight less than 1500 g, may have been influenced by other factors. It needs to be taken into consideration that, over the study period, the bed occupancy rates in the two neonatal intensive care units were high and there were inadequacies regarding the physical facilities, the professional staff per bed ratio and the materials available. In an analysis over a 15-year period conducted in a similar institution in Brazil, it was observed that the peri-intraventricular hemorrhage rate declined from 50.9% in 2001 to 11.9% in 2005, despite an increasing survival rate among extremely premature newborns. In that study, changes to the neonatal intensive care unit that took place during the study period (acquisition of equipment, hiring of professionals and contracting of specialized services) were considered to be important factors in that result [17].

In the present study, no statistically significant associations were found for any of the obstetric or perinatal risk factors, which all presented p-values > 0.05. However, it had previously been reported that newborns whose mothers had been diagnosed with chorioamnionitis were at significantly higher risk of peri-intraventricular hemorrhage [2] [18]. In the present study, the analysis on this factor was probably impaired by the small number of patients who presented chorioamnionitis or by underreporting, given that the diagnosis was based on a clinical assessment, without any histological analysis.

It is important to note that the frequency of antenatal use of corticoids as a protective factor was low (29.5%), in comparison with the frequency presented in the 2014 annual report of the Brazilian Network for Neonatal Research (77.0%) [7]. This result can possibly be explained by the high number of newborns in the present study who had been transferred from other hospitals (32.7%). Araujo *et al.* [19] observed that the rate of corticoid use in the population transferred from elsewhere was 24%, while it was 72.7% among newborns delivered in the hospital of their study. Moreover, we used data from two or more doses of corticoids, [18] [20] [21] given that some studies have shown that use of only one dose of this medication did not give rise to any significant difference in the incidence of peri-intraventricular hemorrhage [18] [21].

From studying the neonatal risk factors, it could be seen that gestational age less than 28 weeks and birth weight less than or equal to 1500 g were the dominant factors, thus corroborating the data in the literature [12] [14] [22].

In analyzing the relationship between the Apgar index and peri-intraventricular hemorrhage, it was observed that 46.1% of the newborns who presented Apgar < 7 in the 5th minute of life also presented the severe form of the disease. This result was concordant with the data in the literature [2] [15] [21].

An association between peri-intraventricular hemorrhage and reanimation in

the delivery room has been described in the literature. This was due to changes to the cerebral blood flow: initially through the presence of hypoxia and subsequently through reperfusion after cardiopulmonary reanimation [5] [14]. In the present study, higher frequency of peri-intraventricular hemorrhage was observed among the newborns who underwent reanimation in the delivery room than was reported by other authors [2] [21]. This difference may have been related to the lack of adequate support for reanimation in the delivery room that the institutions of the present study were experiencing at the time of this study.

In the present study, no significant differences relating to peri-intraventricular hemorrhage and transportation between hospitals were seen. Longhini *et al.* [23] conducted a case-control study to evaluate neonatal morbidities in relation to transfers and did not observe any impact of the frequency of peri-intraventricular hemorrhage. However, in a case-control study conducted in China, in which gestational ages and birth weights of premature newborns were paired, a statistically significant relationship between transportation of newborns between hospitals and occurrences of peri-intraventricular hemorrhage was observed [15]. Therefore, it has been suggested that deliveries of premature newborns should be done at tertiary-level centers, so as to avoid transportation between hospitals [15] [19] [23].

Regarding morbidities and treatments among the newborns of the present study, the high frequencies of peri-intraventricular hemorrhage among the newborns with the following conditions can be highlighted: respiratory distress syndrome, sepsis, use of exogenous surfactants (albeit without any difference between doing this in the delivery room and doing it in the neonatal intensive care unit), catheterization of the umbilical vein, mechanical ventilation and blood transfusion. These morbidities and treatments increase the velocity of cerebral blood flow and lead to greater risk of bleeding [5], and this has also been observed by other authors [1] [14] [20] [21] [22] [23] [24].

The frequency of neonatal sepsis was high in the population of the present study, compared with what had previously been seen in other studies [2] [14] [21]. This difference may have been related to how sepsis was classified, considering that in the present study, it was classified clinically. It is possible that in reality the estimates should be higher, beyond what was seen in each neonatal intensive care unit, given that some of these units, like those of the present study, maintain occupation levels much above their capacity, because of a shortage of beds in the state of Alagoas. This would thus increase the possibility of complications among the newborns.

In assessing intra-hospital outcomes, it was seen that the newborns with peri-intraventricular hemorrhage had longer duration of assisted ventilation and longer hospital stay. Presence of greater severity of the disease was associated with higher frequency of death, and this finding was consonant with the data in the literature [12] [14] [18] [20] [25] [26] [27].

Among the limitations of the present study, the time at which the first ultra-

sound examination was performed should be highlighted. This is important in evaluating the obstetric and perinatal risk factors within the first hours of life. In the present study, this examination was done no later than the fourth day of life.

This study was the first of its kind in the State of Alagoas, Brazil. Although the present data do not show new discoveries, the knowledge of the profile of preterm newborns with peri-intraventricular is important for its control, since advances in perinatal and neonatal medicine provide the possibility of greater viability for extreme preterm infants. Future studies could be directed towards neurological evaluations on these newborns.

5. Conclusion

In conclusion, the present study showed that there was high prevalence of peri-intraventricular hemorrhage, and especially of severe forms of this condition. Perinatal and neonatal factors were associated with greater risk of developing peri-intraventricular hemorrhage, and the intra-hospital outcomes studied were more frequent among the newborns with this disease.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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