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Antenatal corticosteroid treatment for the prevention of peri-intraventricular haemorrhage in preterm newborns: a retrospective cohort study using transfontanelle ultrasonography

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Keywords

corticosteroid, intraventricular haemorrhage, prematurity, transfontanelle ultrasonography

Abstract

Objective: The objective of this study was to assess the correlation between antenatal corticosteroids and peri-intraventricular haemorrhage (PIVH) using transfontanelle ultrasonography, as well as to evaluate the risk factors for its incidence. **Methods:** We performed a retrospective cohort study using medical records of preterm newborns. The protocol for maternal corticoid administration for foetal lung maturation included dexamethasone 4 mg (intramuscular) 8/8 hours per 48 hours, with one cycle per week. The diagnosis of peri-intraventricular haemorrhage was based on transfontanelle ultrasonography, using the Papile's classification. The following risk factors for peri-intraventricular haemorrhage were assessed: birth weight, gestational age at delivery, type of delivery, newborn's sex, surfactant administration, premature rupture of membranes and previous history of infection during the current pregnancy. The student's t-test and chi-square test were used for statistical analysis. **Results:** Our sample population included 184 preterm newborns. Transfontanelle ultrasonography revealed peri-intraventricular haemorrhage in 32 (74.4%) and periventricular leukomalacia in 11 (25.6%) newborns. Grade I haemorrhage was found in 20 (62.5%), grade II in five (15.6%), and grade III in seven (21.8%) newborns, as in accordance with Papile's classification. Vaginal delivery ($p = 0.010$), birth weight <1500 g ($p = 0.024$), gestational age at delivery ≤ 32 weeks ($p = 0.018$), and previous history of infection during pregnancy ($p = 0.013$) were considered risk factors for peri-intraventricular haemorrhage in preterm newborns. **Conclusion:** Maternal corticoid administration for foetal lung maturation showed a protective effect against peri-intraventricular haemorrhage in preterm newborns. The risk factors for peri-intraventricular haemorrhage were determined.

Introduction

Prematurity is the main cause of neonatal morbidity and mortality and is associated with severe, major neurological conditions, such as intraventricular haemorrhage grades 3–4, periventricular leukomalacia, and retinopathy of prematurity grades 3–4⁽¹⁾. Intraventricular haemorrhage (IVH) is the main complication in premature newborns and has an incidence of 45% in premature neonates with a body weight of 500–750 g⁽²⁾. IVH occurs in the periventricular germinal matrix, which is the most fragile vascular brain region in premature infants. Furthermore, IVH may occur due to cerebral blood flow disturbance as well as platelet and coagulation disorders. The risk factors for IVH include vaginal delivery, low Apgar score, severe respiratory distress syndrome, pneumothorax, hypoxia, hypercapnia, seizures, patent ductus arteriosus, thrombocytopenia, and infection^(3,4). The majority of preterm newborns with IVH are asymptomatic and the diagnosis is based on cranial ultrasound screening. Severity classification is based on the location and the extent of IVH. The most commonly used classification is the one proposed by Papile⁽⁵⁾.

Antenatal corticosteroid therapy reduces the rates of major neonatal morbidities, respiratory distress syndrome, IVH, and necrotizing enterocolitis as well as limits the need for respiratory support and intensive care admissions⁽⁶⁾. Furthermore, antenatal corticosteroids reduce the risk of moderate cerebral palsy⁽⁷⁾.

The objective of this study was to assess the correlation between antenatal corticosteroid therapy and peri-IVH, as well as the risk factors associated with its incidence in a reference hospital in the northeast of Brazil.

Materials and methods

We performed a retrospective cohort study using medical records of preterm newborns delivered in a University Hospital in the Northeast of Brazil, between January 2008 and December 2012. The study was approved by the Local Ethic Committee (approval no 001087/2013-60); no consent form was required as it was a retrospective study.

The inclusion criteria were as follows: preterm newborns from singleton pregnancies between 22w0d and 34w6d gestation; intact membranes or premature rupture of membranes. The exclusion criteria were as follows: newborns with chromosomal abnormalities or structural anomalies and maternal antenatal corticoid therapy for any reason other than to induce foetal lung maturation. The protocol for maternal corticoid administration for foetal lung maturation included dexamethasone 4 mg (intramuscular) 8/8 h per 48 h, with one cycle per week.

The diagnosis of peri-IVH was based on transfontanelle ultrasonography performed using Tosbee apparatus (Toshiba, Tokio, Japan) equipped with a micro convex (5 MHz) and liner probes (8 MHz). Ultrasound assessments were performed by an experienced examiner using the bregmatic fontanelle as an acoustic window in sagittal, axial, and coronal views to view the ventricular system and brain parenchyma. The first transfontanelle ultrasonography was performed between day 1 and day 10 after delivery. The second US scan was performed depending on the clinical status of newborns or, in the case of abnormalities detected in the first ultrasound examination, 15 days after the first US scan. If the first US scan was normal, the second one was performed after 30 days. The assessment of PIVH grade was based on the Papile's classification⁽⁵⁾: 1) haemorrhage restricted to the subependymal germinal matrix; 2) subependymal and intraventricular haemorrhage, without ventricular dilatation; 3) subependymal germinal matrix haemorrhage, intraventricular haemorrhage, and ventricular dilatation; and 4) parenchymal haemorrhage associated with intraventricular dilatation. We used first ultrasound findings for statistical analysis.

Data were transferred to Excel 2007 spreadsheet (Microsoft Corp., Redmond, WA, USA) and analysed with Stata version 11.0 (StataCorp LP, College Station, TX, USA). The following risk factors for IVH were assessed: birth weight, gestational age at delivery, type of delivery, newborn's sex, surfactant administration, premature rupture of membranes, and previous history of infection during pregnancy (clinical and/or laboratorial diagnosis). Birth weight was classified into three categories: A (birth weight <1000 g), B (birth weight between 1000 and 1500 g), and C (birth weight >1500 g). Gestational age at delivery was classified into two categories: A (<32 w 0 d) and B (32w0–34w6d). For the descriptive analysis, we used simple frequencies for nominal variables, and the position (mean) and dispersion [standard deviation (SD)] of numerical variables. We used the t-test to compare the mean between the groups and the chi-square test to compare the other qualitative variables. A *p* value (*p*) of < 0.05 was considered statistically significant.

Results

Our sample population consisted of 184 preterm newborns who were hospitalised in the Neonatal Intensive Care Unit of the University Hospital between January 2008 and December 2012. Ninety-seven (53.1%) newborns were males and 87 (46.9%) were females. Transfontanelle ultrasonography revealed abnormalities in 43 (23.3%) of the newborns; normal results were obtained in 141 (76.7%) newborns, 26 (60.5%) were females and 17 (39.5%) were males, with no statistical difference regarding sex (*p* = 0.97).

Transfontanelle ultrasonography revealed peri-IVH in 32 (74.4%) and periventricular leukomalacia in 11 (25.6%) newborns. Grade I haemorrhage was found in 20 (62.5%), grade II in five (15.6%), and grade III in seven (21.8%) newborns, as in accordance with the Papile's classification⁽⁵⁾. Corticoids were administered in 105 pregnant women (57.1%); of those 33 received one cycle, 23 received two cycles, 13 received three cycles, and 23 received four cycles. Among the newborns whose mothers received corticoids during pregnancy, 22 (20.9%) showed abnormalities in the transfontanelle ultrasonography and 83 (79.1%) were normal. In the case of mothers who did not receive corticoid therapy, 21 (26.6%) newborns had peri-IVH and 58 (73.4%) were normal. There was a significant correlation between maternal corticoid administration and the presence of lesions on the transfontanelle ultrasound ($p = 0.048$). Regarding maternal corticoid administration and Papile's classification, we observed an increase in the number of periventricular leukomalacia cases among pregnant women who did not use corticoids, however without statistical difference ($p = 0.57$) (Table 1).

The mean gestational age (\pm SD) at delivery was 32 \pm 2.1 weeks with 29 newborns <32 weeks and 14 \geq 32 weeks gestation, showing abnormalities in the transfontanelle ultrasonography ($p = 0.018$). Regarding the birth weight, 27 (14.7%) newborns had a birth weight <1000 g, 78 (42.6%) had a birth weight of 1000–1500 g, and 78 (42.6%) had a birth weight >1500 g. Regarding the relationship between birth weight and abnormal TF scan, we observed more cases of infants with a weight of 1000–1500 g with a statistical difference ($p = 0.024$). Regarding the type of delivery, there were 76 vaginal deliveries and 108 caesarean sections, with statistical difference between the type of delivery and abnormal TF scan ($p = 0.01$). Regarding the previous history of infection during pregnancy, 67 (36.4%) mothers reported infections, 105 (57.1%) had no history of infection, and 12 (6.5%) had no information on infections in medical records. There was a correlation between the history of infection and TF scan abnormalities ($p = 0.013$) (Table 2).

Discussion

In our study, 184 (17.4%) preterm newborns had peri-IVH, and this rate was consistent with the find-

Variable	TFUS Normal n (%)	TFUS Abnormal n (%)	P Value
Gestational age at delivery			0.018
≤32 weeks	65 (69.5)	29 (30.5)	
32–34 weeks	75 (84.3)	14 (15.7)	
Birth weight			0.024
≤1000 g	16 (59.3)	11 (40.7)	
1000–1500 g	59 (75.6)	19 (24.4)	
≥1500 g	66 (84.2)	12 (15.3)	
Type of delivery			0.010
Vaginal	51 (67.1)	25 (32.9)	
Caesarean	90 (83.4)	18 (16.7)	
Surfactant administration			0.374
Yes	73 (73.0)	27 (27.0)	
No	66 (81.5)	15 (18.5)	
No information	2 (66.7)	1 (33.3)	
Premature rupture of membranes			0.162
Tak	34 (69.4)	15 (30.6)	
Nie	107 (79.3)	28 (20.7)	
Previous history of infection			0.013
Yes	53 (79.1)	14 (20.9)	
No	83 (79.0)	22 (20.9)	
No information	5 (41.7)	7 (58.3)	

TFUS – transfontanelle ultrasonography

Tab. 2. Correlation between abnormalities in transfontanelle ultrasonography and factors associated with preterm birth

ings of Farange and Assis, who observed PIVH incidence rate of 15% in a University Hospital in the southeast of Brazil⁽⁸⁾. Periventricular haemorrhage was more frequent (62.5%), and 37.49% of the most severe cases corresponded with IVH. Hence, the majority of neurological vascular lesions were classified as Papile grade I, which is consistent with Mancini et al.⁽⁹⁾ who found incidences of up to 70% for Papile grade I.

Variable	Papile I n (%)	Papile II n (%)	Papile III n (%)	PVL n (%)	P Value
Maternal corticoid therapy					0,57
Present	12 (54.5)	1 (4.5)	3 (13.6)	6 (27.2)	
Absent	8 (38.0)	4 (19.1)	4 (19.1)	5 (23.8)	

PVL – periventricular leukomalacia

Tab. 1. Correlation between maternal corticoid administration and the presence of periventricular leukomalacia graded according to the Papile scoring system, as revealed by transfontanelle ultrasonography

In the present study, maternal corticoid administration to accelerate foetal lung maturation showed a protective effect against PIVH in preterm newborns, which is consistent with previous studies^(10,11). More severe cases occurred in preterm newborns whose mothers did not receive antenatal corticoids; however, without statistical difference. In our study, we used weekly cycles of maternal corticoid therapy for foetal lung maturation as this was the current protocol at the time of our study (January 2008 and December 2012). In the beginning of 2013, the protocol was changed and included only one cycle of four 6mg dexamethasone doses (intramuscular) at 12-hour intervals. The choice of dexamethasone is a consequence of a systematic review which showed lower rates of IVH compared to betamethasone in pregnant women with risk of preterm birth⁽¹²⁾.

There was a correlation between peri-IVH and the newborn sex, which was observed in previous studies⁽¹³⁾. In our study, there was a statistically significant correlation between the female sex (60.5%) and peri-IVH, as opposed to Sarker et al.⁽¹⁴⁾ who observed higher incidence among males.

In our study, 57.4% of all preterm newborns had a weight <1500 g and showed a direct correlation with PIVH. Mancini et al.⁽⁹⁾ observed a PIVH incidence rate of 29.8% in preterm newborns with a weight <1500 g. We also observed a significant correlation between PIVH and gestational age at delivery ≤ 32 weeks gestation. Mancini et al.⁽⁹⁾ observed the gestational age of 30 weeks as the cut-off with a PIVH rate of 47.3%.

We observed a significant correlation between vaginal delivery and PIVH, proving the protective effect of caesarean section in preterm foetuses mainly at ≤ 32 weeks gestation. According to O'Shea et al.⁽¹⁵⁾, the most important measure to prevent PIVH was not the type of delivery, but avoiding the second stage of

labour. Similarly, Gawade et al.⁽¹⁶⁾ observed that the risk of mild IVH was increased in preterm newborns exposed to the second stage of labour compared to elective caesarean section, however without statistical significance relative to severe IVH. However, new randomized controlled trials are necessary to prove the protective effect of caesarean section on IVH in preterm newborns. Furthermore, we observed a significant correlation between previous history of infection during pregnancy and PIVH, which was also observed by Harding et al.⁽¹⁷⁾

Our study was limited by a relatively small sample, which included 57.4% of preterm newborns with a weight <1500 g. More severe IVH cases occurred in preterm newborns who did not receive antenatal corticosteroids; however, without statistical significance. We believe that a larger sample size mainly including preterm newborns <32 weeks gestation could prove the real benefit of corticosteroids. Another limitation of this study was related to the weekly cycles of maternal corticoid therapy, which did not allow to verify whether only one cycle ensured a protective effect against PIVH in preterm newborns.

In conclusion, maternal corticoid administration to induce foetal lung maturation showed a protective effect against peri-IVH in preterm newborns. Vaginal delivery, birth weight <1500 g, gestational age at delivery ≤ 32 weeks, and previous history of infection during pregnancy were considered risk factors for peri-IVH in preterm newborns.

Conflict of interest

Authors do not report any financial or personal connections with other persons or organizations, which might negatively affect the contents of this publication and/or claim authorship rights to this publication.

References

- Grisaru-Granovsky S, Reichman B, Lerner-Geva L, Boyko V, Hammerman C, Samueloff A *et al.*: Israel Neonatal Network: Population-based trends in mortality and neonatal morbidities among singleton, very preterm, very low birth weight infants over 16 years. *Early Hum Dev* 2014; 90: 821–827.
- Wilson-Costello D, Friedman H, Minich N, Fanaroff AA, Hack M: Improved survival rates with increased neurodevelopmental disability for extremely low birth weight infants in the 1990s. *Pediatrics* 2005; 115: 997–1003.
- Antoniuk S, da Silva RV: [Periventricular and intraventricular hemorrhage in the premature infants]. *Rev Neurol* 2000; 31: 238–243.
- Ballabh P: Intraventricular hemorrhage in premature infants: mechanism of disease. *Pediatr Res* 2010; 67: 1–8.
- Papile LA, Burstein J, Burstein R, Koffler H: Incidence and evolution of subependymal and intraventricular hemorrhage: a study of infants with birth weights less than 1,500 gm. *J Pediatr* 1978; 92: 529–534.
- Roberts D, Dalziel SR: Antenatal corticosteroids for accelerating fetal lung maturation for women at risk of preterm birth. *Cochrane Database Syst Rev* 2006; 3: CD004454.
- Wong D, Abdel-Latif M, Kent A; NICUS Network: Antenatal steroid exposure and outcomes of very premature infants: a regional cohort study. *Arch Dis Child Fetal Neonatal Ed* 2014; 99: F12–F20.
- Farange L, Assis MC: [Ultrasonic findings of intracranial hemorrhage in preterm neonates]. *Arq Neuropsiquiatr* 2005; 63: 814–816.
- Mancini MC, Barbosa NE, Banwart D, Silveira S, Guerpelli JL, Leone CR: Intraventricular hemorrhage in very low birth weight infants: associated risk factors and outcome in the neonatal period. *Rev Hosp Clin Fac Med Sao Paulo* 1999; 54: 151–154.
- Jodeiry B, Heidarzadeh M, Sahmani-Asl S, Hoseini M, Javaherzadeh H, Eliasi S *et al.*: Study of intraventricular hemorrhage in VLBW neonates admitted in Al-Zahra Hospital, Tabriz, Iran. *Niger J Med* 2012; 21: 92–97.
- Ajayi O, Nzeh DA: Intraventricular haemorrhage and periventricular leukomalacia in Nigerian infants of very low birth weight. *West Afr J Med* 2003; 22: 164–166.
- Brownfoot FC, Gagliardi DI, Bain E, Middleton P, Crowther CA: Different corticosteroids and regimens for accelerating fetal lung maturation for women at risk of preterm birth. *Cochrane Database Syst Rev* 2013; 8: CD006764.

13. Vohr B, Ment LR: Intraventricular hemorrhage in the preterm infant. *Early Hum Dev* 1996; 44: 1–16.
14. Sarkar S, Bhagat I, Dechert R, Schumacher RE, Donn SM: 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 Perinatol* 2009; 26: 419–424.
15. O'Shea TM, Volberg F, Dillard RG: Reliability of interpretation of cranial ultrasound examinations of very low-birthweight neonates. *Dev Med Child Neurol* 1993; 35: 97–101.
16. Gawade PL, Whitcomb BW, Chasan-Taber L, Pekow PS, Ronnenberg AG, Shah B *et al.*: Second stage of labor and intraventricular hemorrhage in early preterm infants in the vertex presentation. *J Matern Fetal Neonatal Med* 2013; 26: 1292–1298.
17. Harris DL, Bloomfield FH, Teele RL, Harding JE; Australian and New Zealand Neonatal Network: Variable interpretation of ultrasonograms may contribute to variation in the reported incidence of white matter damage between newborn intensive care units in New Zealand. *Arch Dis Child Fetal Neonatal Ed* 2006; 91: F11–F16.