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ASSOCIATION OF VARIOUS RISK FACTORS FOR INTRAVENTRICULAR HEMORRHAGE IN PREMATURE NEONATES

[1]*Sheikh Quyoom Hussain, [2]Juvera Gul Wani and [3]Waseem Rafiq

[1,3]Registrar, Department of Paediatrics, GB Pant Hospital, GMC Srinagar.
[2]Registrar, Department of Gynaecology and Obstetrics, L D Hospital, GMC Srinagar.

***Corresponding Author: Dr. Sheikh Quyoom Hussain**
Registrar, Department of Paediatrics, GB Pant Hospital, GMC Srinagar.

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ABSTRACT

Background: Intraventricular hemorrhage (IVH) is a serious complication of premature (<32 weeks) deliveries, especially in very-low-birth-weight (VLBW; <1500 g) neonates. Infants developing severe IVH are more prone to long-term developmental disabilities. We analyzed the risk factors for IVH in preterm VLBW neonates in tertiary hospital in Kashmir india. **Methods:** We included premature infants with IVH (n=92) and gestational age and birth weight-matched control group infants (n=92) admitted to our neonatal intensive care unit. Cases were divided into mild (grades I and II; n=52) and severe (grades III and IV; n=52) IVH groups. Association of IVH with risk factors in the first week of life was investigated. **Results:** The following risk factors were associated with severe IVH: lack of antenatal steroid administration (P<.001), pulmonary hemorrhage (P=.023), inotrope use (P=.032), neonatal hydrocortisone administration (P=.001), and patent ductus arteriosus (PDA) (P=.005) Journal Pre-proof. **Conclusions:** Failure to receive antenatal dexamethasone, PDA, hydrocortisone administration for neonatal hypotension, was associated with severe IVH in VLBW neonates. Clinicians and healthcare policy makers should consider these factors during decision-making.

KEYWORDS: Association of IVH with risk factors in the first week of life was investigated.

INTRODUCTION

During the last few decades, the survival of preterm infants has increased dramatically.[1,2] This improvement is mainly due to advances in perinatal medicine and neonatal intensive care. Nevertheless, the incidence of neurological impairment remains high among preterm survivors. The most important neurological manifestations of brain damage in preterm infants are cognitive and motor disabilities. Periventricular-intraventricular hemorrhage (PV-IVH) is one of the major causes of the development of cerebral palsy and mental retardation, and the incidence ranges from 15% to 40%, depending on the center in spite of the many efforts to reduce the incidence.[3,4]

Bleeding in and around the cerebral ventricles is one of the most serious complications of being born too early. In contrast, such bleeding is rare in babies born at term, even if severely ill. The reasons for the preterm infant's unique vulnerability are partly anatomic and partly pathophysiologic. The site of bleeding is usually from the subependymal germinal matrix. The bleeding may continue, rupture the ependymal lining, and fill and distend the ventricular system.

The World Health Organization defines preterm birth as any birth before 37 completed weeks of gestation (or 259 days from the mother's last menstrual period). Preterm births are further subdivided into low birth weight (LBW; 1500–2500 g), very low birth weight (VLBW; 1000–1499 g), and extremely low birth weight (ELBW; <1000 g).[5] Intraventricular hemorrhage (IVH) is the most serious complication of premature deliveries, especially in neonates with birth weight <1500 g and gestational age <32 weeks, as it leads to short- and long-term morbidities.[6,7] Infants who develop a severe grade of IVH (grades III and IV) are more prone to develop significant long-term developmental disabilities including cerebral palsy and posthemorrhagic hydrocephalus.[8] Approximately 50% of IVH occurs in the first 72 h of life, with <10% occurring after day 5;8,9 however, its severity can increase during the following days. Therefore, head ultrasound (HUS) is performed between days 5 and 7 to catch attention of the last severity grade of IVH. The incidence increases with decreased gestational age and birth weight.[10,11]

Identifying the risk factors and underlying mechanisms for PV-IVH has the potential to allow for the development of effective strategies for prevention of many neurodevelopmental problems of premature

infants. In the United States, approximately 12,000 premature infants develop IVH annually,[7,12] and more than a million deaths occur annually due to the complications of preterm birth.[5]

Known risk factors for IVH in premature infants include intrauterine infection, prolonged labor, male sex, premature rupture of membranes, metabolic acidosis, postnatal resuscitation, early onset of neonatal sepsis, and respiratory distress syndrome.[10,13,14] Our study evaluated the risk factors for IVH in premature infants in the G B PANT hospital, Kashmir india.

METHODS

Study design and patient details

Our study, a retrospective case–control study was conducted at the neonatal intensive care unit (NICU) of the G B Pant hospital Srinagar between January 2013 and June 2016. Neonates born at ≤32 weeks of gestation, with birth weight <1500 g, and admitted to the level 3 NICU were eligible for inclusion in our study. We excluded premature neonates who died before undergoing HUS, were born outside the hospital, had asphyxia, or died within the first 72 hr of life and those who had congenital anomalies. Among the included patients, all premature infants with IVH were divided into two subgroups depending on the IVH grade: mild IVH (grades I and II) and severe IVH (grades III and IV). Then each group was matched 1:1 with the control group comprising patients who did not have IVH. Each group was matched for gestational age (1week) and birth weight (50 g). Our NICU protocol for routine HUS is to perform the first HUS between days 5 and 7 of life. If the findings are abnormal, then HUS is repeated the next week, and if the findings are normal, it is repeated after 1 month. Additional HUS is performed if required. HUS was interpreted by a radiologist who was not involved in the study and was blinded to its objective.

IVH was classified into grades I to IV according to Papile et al.'s IVH classification.11a.

IVH was diagnosed on the basis of the findings of HUS performed between days 5 and 7 of life after birth.[18,19]

All the ultrasound scans were performed by one expert radiologist and checked by another expert radiologist. Transducers of 7.5 and 10 MHz) were used to perform ultrasound in sagittal and coronal planes. Maternal data included demographic information, antenatal history, delivery mode, Apgar score, fetal growth restriction, birth weight, gestational age, maternal hypertension, and premature delivery cause (maternal or fetal indications). Neonatal data included respiratory support, surfactant use, inotrope and hydrocortisone use for treating hypotension in the first week of life, and PDA presence (treated or not treated). If missing, data were extracted from the medical records by our study team, and NICU charts were reviewed to confirm the accuracy of information. All patients whose relevant study data were unavailable were excluded. Our study evaluated the following risk factors for IVH in premature infants in our hospital: antenatal steroid administration, caesarean section, pregnancy-induced hypertension, gestational diabetes mellitus, male sex, respiratory distress syndrome, surfactant use, invasive respiratory support, pneumothorax, pulmonary hemorrhage, inotrope and hydrocortisone use, and PDA presence. For women between 24 and 33 ± 6/7 weeks of gestational age who are at risk of preterm birth, receive two doses of 12 mg intramuscular dexamethasone every 12 h in the presence of the following risk factors: risk of preterm delivery within 1 week, multiple gestations, or premature rupture of membrane. Because most pregnant women who arrived in labor were unbooked, they had not received the aforementioned dexamethasone therapy. Unbooked pregnant women meeting the criteria who arrived in labor were given single-dose 12 mg intramuscular dexamethasone immediately after an obstetrician received them, as recommended by several guidelines.[20,21]

Statistical analysis

All statistical tests were performed and graphs plotted using Statistical Package for the Social Sciences, version 25.0 (SSPS Inc., Chicago, IL, USA). Appropriate statistical tests were applied.

RESULTS

Demographics and patient features

Table 1

Table 1: Shows the clinicodemoghraphic data of cases and controls.

Parameter	Cases(n=92)	Controls(n=92)
Booked	20	22
Birth weight (g)	1070	1085
Gestational age(weeks)	27.3	28
Apgar 1 min	5(0,7)	5(0,7)
Apgar 5 min	7(3,9)	7(2,9)
Acidosis ph	7.27 (0.16)	7.30(0.15)

853 infants were admitted to the NICU in our hospital between January 2013 and June 2016. Of them, 321 had <32 weeks of gestational age and birth weight ≤1500 g. after excluding the babies not fitting the criteria to be included in the study,92 babies were included the case

group with IVH and 92 babies in the control group without IVH.

There were no significant demographic differences between the case and control groups (**Table 1**), and as expected because of matching, mean gestational age (*P* = .372) and mean birth weight (*P* = .919) were comparable.

Risk factors for IVH

Table 2: Shows a comparison of each variable contributing to the risk of any IVH.

Parameters	Total IVH N=92	Control group N=92	P value
Caesarean section	40	47	0.347
Antenatal steroid	44	58	0.007
Male	52	48	0.496
PIH	18	22	0.347
GDM	5	6	0.165
RDS surfactant use	71	60	0.190
Mechanical ventilation	80	71	0.114
pneumothorax	6	2	0.0375
Inotropes	56	42	0.017
hydrocotisone	37	20	0.018
Pulmonary hemmorhage	20	6	0.012
PDA	65	51	0.030

In premature infants with any IVH, significant risk factors were lack of antenatal steroid administration (*P*=.007), pneumothorax (*P*=.037), pulmonary haemorrhage (*P*=.012), use of inotropes (*P*=.017), neonatal treatment with hydrocortisone (*P*=.018), and presence of PDA (*P*=.030).

Table 3: Shows a comparison of each variable contributing to the risk of mild IVH (grade 1 and 2) and severe IVH(grade 3 and 4).

Parameters	Mild (grade 1&2 IVH) N=50	Control N=50	P value	Severe (3&4) GIVH N=42	Control N=42	P value
Caesarean section	26	27	0.45	14	20	0.56
Ante natal steroid	27	28	0.93	17	30	0.001
Male	30	25	0.34	22	23	0.96
PIH	12	14	0.67	6	10	0.32
GDM	4	4	0.198	1	2	0.57
RDS surfactant use	38	26	0.34	33	34	0.45
Mechanical ventilation	41	30	0.145	39	41	0.50
pneumothorax	4	0	0.98	2	2	0.10
Inotropes	22	15	0.18	34	27	0.032
hydrocotisone	9	9	0.10	28	11	0.001
Pulmonary hemmorhage	7	4	0.21	13	1	0.023
PDA	33	26	0.62	32	25	0.03

In premature infants with severe IVH, significant risk factors were lack of antenatal steroid administration (*P*<.001), pulmonary hemorrhage (*P*=.023), use of inotropes (*P*=.032), neonatal treatment with hydrocortisone (*P*=.001), and presence of PDA (*P*=.03).

DISCUSSION

We aimed to identify risk factors for IVH in premature infants in our hospital covering a vast population in kashmir. We found that lack of antenatal steroid administration and neonatal hydrocortisone administration was significantly associated with severe IVH; this finding is consistent with previous studies.22 Our data revealed that antenatal steroids significantly reduced the percentage of severe IVH, but not mild IVH, in VLBW infants. These results point to the importance of antenatal care, particularly antenatal steroids, in preventing severe IVH. Most cases of mild IVH occur between days 3 and 4 of life, indicating that neonatal care and management in NICU are directly related to the occurrence of mild IVH.

Antenatal steroids do not have a major role in preventing mild IVH. A recent Cochrane review has shown that a single course of antenatal steroids significantly reduces the rate of IVH among premature infants (relative risk

0.55, 95% CI 0.40–0.76).[15] However, it did not discuss the relationship between the timing of IVH and the antenatal steroids. Consistent with the results of this study JU YOUNG et al, antenatal steroid treatment has been reported as conferring protection against the development of PV-IVH.[17] The mechanisms by which corticosteroids decrease the risk of hemorrhage are unclear, but they appear to be independent of enhanced pulmonary maturation. The postulated effects include an anti-angiogenic effect with inhibition of microvessel morphogenesis in the germinal matrix capillary network and stabilization of the microvasculature of the developing germinal matrix.[17] In our study, multivariate analysis showed that PDA was a risk factor for severe IVH in premature infants, consistent with many studies.[18,19] PDA causes fluctuation in cerebral blood flow; prophylactic treatment of PDA with indomethacin on the first day of life in extremely premature infants can reduce severe IVH incidence by enhancing cerebral autoregulation and preventing pulmonary hemorrhage, an identified risk factor for severe IVH in our study and previous studies.[20] Despite this strong evidence of the efficacy of prophylactic treatment of PDA in decreasing severe IVH incidence, we do not routinely give indomethacin on the first day of life for many reasons: (1) it does not improve the survival rate and neurosensory impairment at 18 months of corrected age21; (2) possibility of thrombocytopenia or platelet dysfunction on the first day of life; (3) presence of oliguria or acute kidney injury on the first day of life; and (4) ibuprofen or acetaminophen has the same efficacy as indomethacin in treating significant PDA with fewer side effects.[21]

We also found hydrocortisone administration to be a risk factor for severe IVH among VLBW infants. We administer intravenous hydrocortisone 3 mg/kg/day divided every 8 h for treating premature infants with refractory hypotension in the first days of life.[22] Although fluid volume bolus is the first-line treatment for neonatal hypotension, nonresponders are given inotropes to improve cardiac contractility and cardiac output. Hydrocortisone is then used as the third-line treatment.[22] Both saline boluses and inotropes are well known to be associated with severe brain injury. Because we usually administer hydrocortisone after initiating volume boluses and vasopressors, it was found to be associated with IVH in our study. In the absence of autoregulation, the systemic blood pressure becomes the primary determinant of cerebral blood flow and pressure, which is a pressure-passive circulatory situation. Rapid volume expansion with blood products or hypertonic solutions and excessive use of inotropes for the correction of hypotension results in a rapid increase of cerebral blood flow and can cause injury to fragile germinal matrix capillaries.[5,23,28,29] More research remains to be performed to determine proper criteria or detailed methods for neonatal intensive care that minimize the rapid alteration of hemodynamics of preterm infants. Our study has many limitations. First, this was a retrospective case–control study. Second, we could not measure all the potential confounding variables because most pregnant women were not followed up at our maternity hospital.

CONCLUSION

Severe IVH in VLBW neonates is associated with failure to give antenatal steroids, presence of PDA, and hydrocortisone given for neonatal hypotension. Clinicians and healthcare policy makers should consider these factors during decision-making; for example, coverage of (complete) antenatal steroid therapy should be expanded to reduce the incidence and severity of neonatal IVH. Further studies in a larger population of neonates are required to evaluate all the possible risk factors that may be peculiar to this population.

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