ORIGINAL ARTICLE

Risk factors for intraventricular haemorrhage in preterm infants from a tertiary care hospital of Karachi, Pakistan

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Abstract

Objective: To determine the incidence of Intraventricular Haemorrhage in pre-term infants, along with adverse neonatal outcomes associated with the disease..

Methods: The retrospective case control study was conducted at Aga Khan University Hospital, Karachi, and comprised patients' records from January 2004 to December 2009 of preterm babies from 26-35 weeks of gestation who had Intraventricular Haemorrhage of any grade. The diagnosis was confirmed by ultrasound scan. Controls were preterm births matched with the cases according to gestational age (±1 week) and birth weight (±150 grams). SPSS 19 was used for statistical analysis.

Result: Of the total 201 preterm babies in the study, there were 67(33.33%) cases and 134(66.66%) controls; the respective ratio being 1:2.The incidence of Intraventricular Haemorrhage in the study population was 22.1 per 1000 live births. The odds of developing Intraventricular Haemorrhage was substantially higher in babies with respiratory distress syndrome (odds ratio: 3.77; 95% Confidence Interval: 1.52-9.37; p<0.004) and who were given mechanical ventilation (odds ratio: 23.6; 95% Confidence Interval: 5.09-109.5; p<0.001). There was a four-fold increase in risk of Intraventricular Haemorrhage in babies who received surfactant administration (odds ratio: 4.26; 95% Confidence Interval: 1.77-10.22; p<0.001).

Out of 67 cases, 50(74.6%) re-demonstrated the same grade, 13 (19.4%) were resolved, and 4(6%) progressed. Overall, there were 38 death; the mortality rate being 56.71.

Conclusion: The risk of Intraventricular Haemorrhage was substantially higher in preterm neonates with respiratory distress syndrome, etc., and the mortality rate was higher in babies with severe disease.

Keywords: Intraventricular Haemorrhage (IVH), Preterm infants, Risk factors, Incidence, Neonatal mortality. (JPMA 64: 1146; 2014)

Introduction

Intraventricular Haemorrhage (IVH) is an important cause of perinatal morbidity and mortality in very low birth weight (VLBW) infants. Although the incidence of IVH is decreasing, it is still a serious problem as there is overall increase in preterm births worldwide.[1] According to literature, almost 25%-40% of infants below 1,500 grams of birth weight suffer from IVH and approximately 15% of them might develop severe IVH.[1,2] Although mild IVH (grade I and II) is more subclinical than severe IVH, but it can also cause long-term neurodevelopment deficits such as impairment of specific cognitive abilities.[3]

In literature, various risk factors have been identified in the development of IVH: low birth weight (LBW), gestational age, maternal smoking, breech presentation, gender, premature rupture of membranes, intrauterine infection, mode of delivery, prolonged labour, resuscitation and intubation, transfer from one unit to another, and early onset of sepsis.[4-7] Almost all periventricular/IVH (P/IVH) occurs in the first four days of birth, and a proportion of these P/IVHs are present within the first few hours after birth.[8] It is likely that these early P/IVH have risk factors that relate to the intrapartum period, whereas those that occur after the first day may well relate to early post-natal haemodynamic factors.[9]

The institutional neonatal intensive care unit (NICU) provides tertiary level care to new-borns not only from Karachi, but from other parts of the country as well. The unit receives significant number of preterm babies (<2500 grams) every year. So far, no data is available regarding the incidence and risk factors for IVH in our hospital. To the best of our knowledge, no study on IVH in premature babies has been published from Pakistan. In this study, we aimed at determining the incidence of IVH in our cohort along with adverse neonatal outcomes associated with the disease. We also planned to compare mortality of each

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IVH grade, and to obtain the number of resolved, progressed and re-demonstrated cases.

Patients and Methods

The retrospective case-control study was conducted at Aga Khan University Hospital (AKUH), Karachi, and comprised record of patients from January 1, 2004 to December 31, 2009. Using Epiinfo software, a sample of 201 neonates (both cases and controls) was worked out in order to detect a difference in morbidity at a significance level of 0.05 with 80% power.[5] Cases were defined as neonates born between 26-35 weeks of gestation with the findings of IVH of any grade, whereas the findings of IVH were confirmed by ultrasound scans. Controls were the preterm births matched with the cases according to gestational age (± 1 week) and birth weight (± 150 grams).

Data reviewed included labour room management system, discharge summary, and NICU record. Data was retrieved from patient's medical record in a structured questionnaire, which entailed information about prenatal demographics, such as mother's age, parity, gravida, obstetric complications like hypertension, urinary tract infection (UTI), gestational diabetes, chorioamnionitis, premature rupture of membranes (PROM), conception method, and mode of delivery etc. Gestational age was calculated on the basis of last menstrual cycle/ ultrasound and by post-natal examination (Ballard scoring). All the data was obtained by reviewing the clinical notes of the attending obstetrician and neonatologists. From the neonatal section we retrieved information about baby weight, date of birth, Apgar scores, and neonatal complications such as respiratory distress syndrome (RDS), patent ductus arteriosus (PDA), mechanical ventilation, sepsis, surfactant administration, and pneumothorax.

Incomplete medical records, or those with major/lethal congenital anomaly, and multiple gestations were excluded. The study obtained approval from the institutional ethical review committee. Routine ultrasound brain was performed in all preterm neonates. Controls were ruled out by normal ultrasound having no evidence of IVH, and cases were selected with the evidence of IVH of different grades from grade I to grade IV. The frequency of ultrasound depended on clinical course. The images were obtained by using a high resolution (7.5 MHz) real time scanner in both coronal and sagittal projections through the anterior fontanel. Chest X-ray was done for the diagnosis of RDS and pneumothorax. Echo was performed to assess PDA. The grading system for haemorrhages on ultrasound was done as previously reported.[10] Grade I: Blood in the periventricular germinal matrix regions; Grade II: Blood within the lateral ventricular system without ventricular dilatation; Grade III: Blood within and distending the lateral ventricles; Grade IV: Blood within the ventricular system with dilatation and parenchymal involvement. The definitions of variables were based on pre-set definitions in literature: Prolong rupture of membranes: If rupture of membrane was >18 hours; RDS: If the baby required oxygen at 6 hours of life, along with an abnormal chest X-ray within age 24 hours, consistent with surfactant deficiency;[11] PDA: It was diagnosed clinically on the basis of continuous or systolic murmur in the left sub-clavicular area, associated with hyperactive precordium with wide pulse pressure or bounding pulses. It was echocardiographically significant when the ductal size was >1.5mm or the left atrial to aortic root ratio was <1.4;[12] Sepsis: Physician documented episode of tachycardia/bradycardia, apnoea, hypotension, hyper/hypothermia, hyper/hypoglycaemia or any other sign of systemic illness, with or without positive blood culture, was labelled as sepsis;[13] and UTI: Clinical symptoms and /or evidence of bacteria, nitrites and leukocytes esterase, with or without positive culture.

Data was entered and analysed by SPSS 19. Maternal and neonatal demographics were noted, and all obstetric and neonatal complications along with pregnancy outcome were entered as dichotomous variable (yes/no). We obtained odd ratios (OR) of neonatal outcomes by using conditional logistic regression analysis. We used antenatal steroids, chorioamnionitis, preterm premature rupture of membrane (PPROM), mode of delivery, gestational diabetes, hypertension, as covariates. P less than 0.05 was considered significant.

Results

Out of the total 24,742 deliveries during the study period, 3,426 (13.8%) were preterm births. The incidence of IVH birth in our study population was 22.1 per 1000 live births. There were no significant difference in mean maternal age, gestational age and birth weight in cases and controls. Mode of delivery in both of the groups were predominantly caesarean section (70.1% (n=106) in cases compared to 79.1% (n=47) in controls). The mortality rate among IVH was substantially high (56.7% [n=38] vs. 14.9% [n=20]). Of the 67 babies with the findings of IVH, 60 (89.5%) cases were of low birth weight (<1500 grams), and of these LBW preterm babies the mortality was nearly 53.7% (n=36). There were five cases (7.5%) of assisted reproductive techniques (vs. 7 controls [8.9%]),and of them 04(80%) expired.

The risk of developing IVH was three-fold higher in

preterm baby with RDS diagnosis (OR 3.77; 95% CI 1.52-9.37; p=0.004). Babies who were put on mechanical ventilation had 23 times higher odds of IVH (OR 23.6; 95% CI 5.09-109.5; p<0.001). Babies with diagnosis of IVH had 4 times greater chances of receiving surfactant than the non-IVH counterparts (OR 4.26; 95% CI 1.77-10.22; p<0.001). Although results of PDA and sepsis showed higher odds of developing IVH, but the findings were statistically not significant (Table-1).

Of the 67 cases, 33(49.3%) were initially diagnosed as grade I, out of which 8(24.2%) resolved completely and 2(6.06%) progressed from grade I to grade III and IV respectively. There were 11 (16.4%) cases diagnosed as grade II out of which 4(36.4%) resolved completely and 1(9.09%) case progressed to grade IV. Cases diagnosed initially with grade III were 15 (22.4%), of which only 1(6.7%) resolved and 1(6.67%) progressed to grade IV. Eight (11.9%) cases were diagnosed as grade IV and none of them got resolved (Table-2).

Mortality of cases from grade I-IV who had resolved, progressed or re-demonstrated the same findings were noted separately (Table-3). The mortality rate of IVH

Table-1: Maternal and Neonatal characteristics.

	IVH (n = 67) Frequency (%) Mean ± SD	Non-IVH (n = 134) Frequency (%) Mean ± SD	OR (95% CI)	P value
Maternal characteristics				
Maternal Age	28.7 ± 4.23	28.6 ± 4.80		
Gestation age	29.25 ± 2.2	30.1 ± 2.2		
Mode of delivery				
SVD	20 (29.9)	28 (20.9)		
Caesarean Section	47 (70.1)	106 (79.1)		
Conception				
Spontaneous	62 (92.5)	122 (91.1)		
ART[1]	5 (7.5)	12 (8.9)		
Outcome				
Discharged	29 (43.3)	114 (85.1)		
Expired	38 (56.7)	20 (14.9)		
Neonatal complications[2]				
Birth weight	1170 .87 ± 394.0	1253.30 ± 351.6		
RDS	51 (76.1)	55 (41.0)	3.77 (1.52 - 9.37)	0.004
Sepsis	20 (33.3)	28 (21.2)	1.18 (0.78 - 1.79)	0.418
PDA	15 (22.3)	11 (8.2)	1.581 (0.68 - 3.64)	0.283
Mechanical Ventilation	43 (64.1)	19 (14.1)	23.62 (5.09 - 109.59)	0.000
Surfactant	45 (67.1)	40 (29.8)	4.26 (1.77 -10.22)	0.001

[1]Assisted reproductive technique (IVF and medicine).

[2]OR are obtained from conditional logistic regression. maternal complications were used as covariates.

IVH: Intraventricular Haemorrhage

SVD:Spontaneous Vaginal Delivery

RDS: Respiratory Distress Syndrome

PDL: Patent DuctusArteriosus.

Table-2: Cases diagnosed with different grades of IVH.

IVH grade	Frequency N (%)	Progression of IVH from grade			Re-demonstration of the same grade N(%)	Resolved cases N (%)	Outcome	
		II	III	IV			Expired	Alive
I	33 (49.3)	-	01	01	23 (69.7)	08 (24.2)	15 (45.5)	18 (54.5)
II	11 (16.4)	-	-	01	06 (54.5)	04 (36.4)	05 (45.5)	06 (54.5)
III	15 (22.4)	-	-	01	13 (86.7)	01 (6.7)	10 (66.7)	05 (33.3)
IV	08 (11.9)	-	-	-	08 (11.9)	-	08 (100)	-
Total	67		01	03	50	13	38	29

IVH: Intraventricular Haemorrhage.

Table-3: Mortality of different grades.

Grade	Resolved (N %)		Re-demonstrated (N%)		Progressed (N %)	
	Alive	Expired	Alive	Expired	Alive	Expired
Grade I	7/8 (87.5)	1/8 (12.5)	10/23 (43.5)	13/23 (56.5)	1/2 (50)	1/2 (50)
Grade II	4/4 (100)	0/4	2/6 (33.3)	4/6 (66.7)	0/1	1/1 (100)
Grade III	1/1 (100)	0/1	4/13 (30.8)	9/13 (69.2)	0/1	1/1 (100)
Grade IV	-	-	-	8/8 (100)	-	-
Total	12/13	1/13	16/50	34/50	1/4	3/4

cohort was directly proportional to IVH grades. Of the eight cases resolved at grade I, 1(12.5%) expired. Amongst the re-demonstrated cases, mortality was increasing with increasing grade. Of the 8 cases re-demonstrated at grade IV, none survived. There were four cases of progressed IVH, out of them 3(75%) expired.

Discussion

IVH is a common neonatal morbidity among premature infants which is diagnosed by cranial ultrasound. In the recent era there is improved survival of preterm babies because of good antenatal care and postnatal management of potential complications associated with prematurity. Still, IVH in preterm babies can lead to significant neurologic disability. They are at high risk of seizures, hydrocephalus, and death in the new-born period.

Previous studies showed incidence of IVH around 15%-40% which is comparable to our results.[3,14] In a recent study from China the incidence of IVH in babies <34 weeks was 3.9%.[15] Thus, we report a decrease in the incidence of IVH over the years as also reported in recent literature.[15] The incidence of IVH was correlated with the presence of possible neonatal, obstetrical, or therapeutic risk factors. The significant risk factors for IVH in this study were low Apgar score at five minutes, sepsis, RDS, pneumothorax, and ventilator support.

In babies who have severe RDS and are on mechanical ventilation, with higher ventilator settings, there is an increase in the cerebral venous pressures or fluctuating cerebral blood flow velocity which increases the risk of IVH. This study also showed increased risk of IVH in babies who were on mechanical ventilation consistent with previous studies.[13-15] Pneumothorax is more common in babies with severe IVH, this was not a direct risk factor, but babies who had severe RDS and on high ventilator settings had greater risk of IVH. Similar results have been found in a recent study from Iran.[16]

In a recent study carried out to identify risk factors for IVH apart from birth weight and gestational age, it was reported that IVF and sepsis increased the risk of IVH.[16] Another study reported that early sepsis was associated with an 8-fold increase in the incidence of IVH.[17] In our study, a high number of babies with IVH had sepsis, but there was no significant relation found between IVH and In vitro fertilization (IVF). IVF is still not a very accepted method of conception in our culture, and a small number of couples opt for this method of conception when compared with the developed world.

This study showed high mortality rate of 68% in advanced IVH. The higher mortality rate of grades III and IV was comparable with earlier findings.[5] The adverse neurological outcomes are reported to be associated with grade III and grade IV IVH. The study accentuates a need to conduct a long-term neurodevelopment outcome of IVH infants in our cohort.

Our result contradicts that male gender, vaginal delivery and artificial conception increases the risk of IVH, as found in many studies. Various studies showed that male babies are at greater risk of developing IVH and severe IVH, but not Periventricular leukomalacia (PVL).[17] A study showed that male infants are more susceptible to adverse outcomes of prematurity.[18] Our study contradicts this and there was no gender difference in the occurrence of IVH in preterm babies. Various studies have been carried out to see if caesarean section has benefit over vaginal delivery and it showed conflicting results. One study showed that babies born vaginally were more likely to develop IVH than those delivered by caesarean section.[19]

The current study had several limitations. The data was a retrospective review and had a small sample size.

Conclusion

IVH is still very common in our setting though we do not know the exact morbidity associated with it. IVH births are at increased risk of RDS, pneumothorax, and mechanical ventilation. Mortality rate of the study group was directly proportional to the grade at which it was diagnosed. A larger cohort study will help to determine the prevalence of the disease and obtain the long-term neuro-

developmental outcome associated with IVH babies.

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