Risk Factors of Subependymal Hemorrhage-Intraventricular Haemorrhage in Preterm Infants

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Abstract

Background: To determine the frequency and peak time of occurrence of subependymal hemorrhage-intraventricular hemorrhage (SEH-IVH) in preterm infants and to identify the predisposing risk factors.

Methods: In this descriptive study consecutive live born babies (n=135), between the gestational ages of 28-34 weeks, were enrolled. Information regarding weight, gestational age, mode of delivery and presence of risk factors were recorded. Each newborn underwent cranial ultrasound on designated days and was followed up till the fourth week of life unless expired.

Results: The frequency of SEH-IVH was found to be 20.8%. The most vulnerable group in terms of gestational age and weight were infants < 32 wks and weighing < 1.5 kg respectively. The peak age of occurrence of SEH-IVH was first three days of life. Risk factors found to be associated with SEH-IVH were RDS with ventilation, exchange transfusion and thrombocytopenia.

Conclusion: The incidence of SEH-IVH in infants between 28-34 wks gestation is significantly high. The crucial period is the first three days of life and respiratory distress syndrome (RDS) with ventilation, exchange transfusion and thrombocytopenia carry the highest risk of hemorrhage. There is a need to emphasize on the prevention of prematurity and optimum perinatal management to minimize the risk of hemorrhage.

Key words: Subependymal hemorrhage-intraventricular hemorrhage, Premature infants.

Introduction

Subependymal haemorrhage - intraventricular hemorrhage is one of several complications associated with prematurity and carries significant morbidity and mortality. It is principally a problem of very low birth weight infants i.e. infants weighing less than 1.5kg and also those delivered before 32-34wks of gestation.[1-4] With improved obstetric and perinatal management, the incidence of SEH-IVH has shown a significant decline. [5-10] Tertiary centres currently report an incidence between 20-25% in infants born before 34 wks of gestation with figures rising with decreasing weight and gestational age.[2,4,11-25]The incidence of IVH in premature infants between 500g-749g is still very high and is approximately 45% . [26]

Upto 90% of IVH cases evolve in the first 72 hours of postnatal life; 30% in the first 6 hours, 40-60% in the first 24 hours and 60-80% within 48 hours[27-30] Hemorrhage on or after the fourth day of life occurs in 10% of all preterm infants with IVH.[1]Intraventricular hemorrhage has been extensively documented in preterm newborns with respiratory distress syndrome requiring mechanical ventilation.[10,18,31-33] Other well recognized risk factors for IVH include asphyxia, hypercarbia, rapid volume expansion, routine care taking maneuvers, patent ductus arteriosus, high concentration of inspired oxygen, pneumothorax, seizures,anemia, low blood glucose, platelet and coagulation defects.[1,18,31-42] Better understanding of the pathogenesis of IVH has led to several therapeutic interventions aimed at counteracting the known risk factors. Many such interventions like use of antenatal steroids and careful ventilator management have demonstrated a significant reduction in the incidence of IVH.[43-49]In developing countries incidence has been reported to be between 28%-75%.[50-54] More recent data also shows a very wide range between 9%-64.4%.[27, 55-62]

Patients and Methods

This non-interventional, descriptive, analytic study was carried out in the Department of Neonatology, Children's Hospital, Pakistan Institute of Medical Sciences (P.I.M.S), Islamabad from September 2002 to January 2003. During the study period, all consecutive live births delivered at the MCH Centre with gestational ages between 28-34 weeks were enrolled. Weight was measured without clothes and grouped under four categories, namely 0.75kg-1kg, 1.1kg-1.5kg, 1.6kg-2.0kg, and >2.0kg. Gestational age was estimated by dates i.e. last menstrual period or antenatal ultrasound if performed. In the absence of aforementioned information, Dubowitz scoring was used for estimating the gestational age.[63] Groups assigned for gestational age were 28 wks, 29-30 wks,

31-32 wks and 33-34 wks. Babies with gestational age <28 weeks, with weight <750gms and with lethal malformations were excluded from this study. Cranial ultrasonography of selected patients was performed. Images were obtained through the anterior fontanelle in both coronal and right and left parasagittal planes.

Every enrolled infant was followed up for 28 days or till death if earlier. Thirteen babies, without IVH on the first two visits,failed to report for 3rd cranial ultrasonography on the designated days. They were reported as well on telephone by parents. These infants underwent cranial ultrasound examination at least three times, (0-3, 7-10, 21-28 days). Admitted babies, however, had daily ultrasounds till they were discharged or expired. In addition to this, ultrasound was also done whenever clinical indications like abrupt fall in hematocrit, shock, bulging fontanel,i.e., change in the level of consciousness or change in the respiratory support without any other explanation, appeared at any time during admission. IVH was classified into four grades (Gd. I-IV) according to the system of grading reported by Papile; Gd I-isolated SEH, Gd II-rupture into ventricle but no ventricular dilatation, Gd III-rupture into ventricle with ventricular dilatation andGd IV-IVH with parenchymal extension.[64]

Risk factors were defined according to standard recommendations and protocols used in the neonatal unit.Sample size was calculated by using statcalc of software EpiInfo version 6.0 by using descriptive study, random, non-cluster sampling technique. By keeping the population size as 400 (estimated annual deliveries in MCH at the time with gestation of 28-34 weeks) and expected frequencies as 25% and worst expected being 20%, with confidence level of 95%, a sample size of 135 was calculated.Univariate and multivariate analysis was carried out for risk factors to determine their effect on SEH-IVH and Odds ratio with 95% confidence interval were calculated by keeping p-value of < 0.05 as significant.

Results

Of these 135 babies with gestational age of 28-34 weeks, 60% were male and 40% were females. The mean gestational age was 31.4±2.05 weeks. The mean birth weight of study population was 1.59±0.42 kg.Two third of babies were delivered by SVD whereas about 1/3rd (30%) were delivered through C-Section (Table 1).Of the total 135 babies, 28 babies were found to have SEH-IVH on ultrasonography during their neonatal period. Eight babies each had Grade I and Grade II bleed while 5 babies had Grade III and seven had grade IV bleed. Three fourth (21) of

the babies developed SEH-IVH during the 1st three days of life. Of these, again, the majority i.e. 12 out of 21 babies had SEH-IVH within 1st 24 hours of life. Almost all SEH-IVH occurred within the 1st week of life with the exception of one, where the bleeding occurred on 14th day of life (Table 2;Figure 1).Two of the studied risk factors i.e. birth asphyxia and hypoglycemia were not found to be associated with SEH-IVH, while all others including RDS, mechanical ventilation, hypoxia, PDA, high FiO_2, exchange transfusion, anemia and thrombocytopenia were found to be significantly associated with SEH-IVH (Table 3). Thrombocytopenia carried the highest odds ratio, however, RDS with ventilation, exchange transfusion and thrombocytopenia retained their significance independently in multivariate logistic regression (stepwise) model (Table 4).

Table 1: Comparison of demographic factors of premature infants with and without SEH-IVH (n = 135)

| Variables	SEH-IVH (n = 28)	NO SEH-IVH (n = 107)	OR (95%CI), p-value
Sex Male Female	19 (67.9%) 9 (32.1%)	63 (58.1%) 44 (41.1%)	1.47(0.57-3.91) 0.51
Gestational Age Median Mean $\pm$ SD 28 wks	31.0 30.0 $\pm$ 2.0 2 (2.1%)	32.0 31.6 $\pm$ 2.0 5 (4.7%)	1.57(0.21-9.95) 0.96
29 to 30 wks	11 (39.3%)	27 (25.2%)	1.92 (0.73–5.00) 0.21
31 to 32 wks	9 (32.1%)	28 (26.2%)	1.34 (0.49-3.58) 0.69
33 to 34 wks	6 (21.5%)	47 (43.9%)	*0.35 (0.12-1.00) 0.05*
Weight (kg) Median Mean $\pm$ SD 0.75 to 1.0 kg	1.26 1.45$\pm$0.40 1 (3.6%)	1.64 1.63 $\pm$ 0.40 8 (7.5%)	0.46(0.02-3.91) 0.75
1.1 to 1.5 kg	17 (60.6%)	42 (39.3%)	2.39 (0.95-6.12) 0.06
1.6 to 2.0 kg	5 (17.9%)	38 (35.5%)	0.39 (0.12-1.22) 0.11
More than 2.0 Kg	5 (17.9%)	19 (17.7%)	1.01 (0.29-3.28) 0.79
Mode of delivery SVD	18 (64.3%)	73 (68.2%)	0.84 (.32-2.20) 0.86
C-Section	9 (32.1%)	32 (29.9%)	1.11 (0.41-2.94) 0.99
Forceps	1 (3.6%)	2 (1.9%)	1.94 (0.00-28.9) 0.86
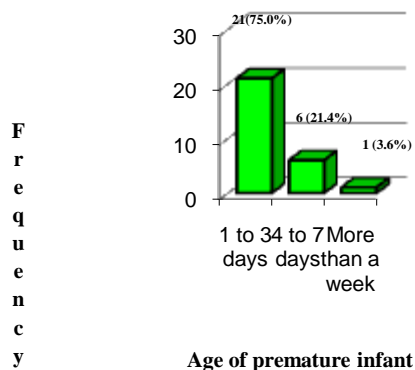
Fig 1: Relationship of age with SEH-IVH

Of these, the babies on assisted ventilation with RDS carried the highest risk of SEH-IVH closely followed by babies undergoing exchange transfusion and thrombocytopenia. Other risk factors like hypoxia, high concentration of O_2, PDA, and anemia lost their significance in multivariate logistic regression analysis.Out of these 28 infants, 20(71.4%) expired and only 8(28.3%) were either discharged or remained admitted beyond 28 days of life. Of this mortality group, majority (12) had grade III and Grade IV bleed while only three babies with Grade I SEH-IVH expired during their stay in the hospital.

Table 2: Frequency of SEH-IVH on days of life(n = 28)

Age in days	Number	Percentage
First day	12	42.8%
Second day	5	17.8%
Third day	4	14.3%
Fourth day	1	3.6%
Fifth day	4	14.3%
Sixth day	1	3.6%
Fourteenth day	1	3.6%

Discussion

The most common form of brain injury in the premature infant is subependymal hemorrhage-intraventricular hemorrhage.Most tertiary care centres from the United States, Australia and other developed countries currently report an incidence between 20-25% in infants born before 34 wks of gestation.[2, 4, 11-18] Data from the developing countries shows a wide range of incidence of IVH in premature infants.Generally the incidence is very high   primarily because of lack of optimum obstetric and perinatal care.[53]

Table 3: Predisposing factors associated with SEH-IVH in premature infants (n = 135)

Variable	SEH-IVH (n = 28)	N0 SEH-IVH (n = 107)	X^2	DF	OR (95% CI), p-value
Birth asphyxia	5 (17.9%)	6 (5.6%)	2.96	1	3.66(0.87-15.2), 0.08
RDS	12(42.9%)	19 (17.8%)	6.55	1	3.47(1.29-9.37) 0.01
Mechanical ventilation	18(64.3%)	15 (14.0%)	27.7	1	11.04(3.91-32.0) <0.00001
Hypoxia	14(50.0%	18 (16.8%)	11.74	1	4.94(1.84-13.39) <0.00001
PDA	3 (10.7%)	1 (0.9%)	4.37	1	12.72(1.10-331.79) 0.03
High concentration of inspired O_2	12(42.9%)	12 (11.2%)	13.11	1	5.94(2.06-17.34) <0.00001
Exchange transfusion	15(53.6%)	21 (19.6%)	11.40	1	4.73(1.79-12.57) <0.00001
Anemia	6 (21.4%)	6 (5.6%)	5.04	1	4.59(1.17-18.18) 0.02
Hypoglycemia	6(21.4)%)	8 (7.5%)	3.27	1	3.38(0.92-12.23) 0.07
Thrombocytopenia	11(39.3%)	3 (2.8%)	27.97	1	22.43(5.93-114.5) <0.00001

Table 4: Risk Factors for SEH-IVH in premature infants by using multivariate logistic regression

Risk Factors	OR (95% CI)	p-Value
RDS with Ventilation	8.21 (2.30 – 28.33)	< 0.00001
Exchange transfusion	7.79 (2.00 – 29.09)	0.003
Thrombocytopenia	5.09 (1.70 – 14.98)	0.002

The most vulnerable group in present study were infants between 28-32 weeks gestation. This inverse relationship between gestational age and SEH-IVH is expected and in accordance with other studies. Dolfin et al reported a significant difference between the incidence of SEH-IVH in infants whose gestational age was less than or equal to 29 weeks compared to infants between 30-34 weeks gestation. Among infants less

than or equal to 29 weeks gestational age 56% had SEH-IVH while only 8% had bleed in the gestational group of 32-34 weeks.[66]

It was seen in the present study that babies between 1.6-2.0 kg had an incidence of IVH of only 12% increasing to 30% in infants between 1.1-1.5 kg. This increasing trend in the frequency with decreasing weight was expected and in accordance with other studies. However, the prevalence of SEH-IVH for infants between 750 gms to 1.0 kg was rather low (11%) in our study because very few babies fell in this group (7% of study population). It was observed that babies > 2 kg did not follow the inverse relationship between weight and frequency and showed a relatively higher incidence (21%). This can be explained by the fact that these babies had other risk factors in addition to being premature. The most vulnerable group prone to SEH-IVH are infants weighing 1.5 kg or less and the incidence increases with decreasing birth weight.[26,51,67] Studies revealed that more than 95% of the bleeds occurred during the first week of life. [60,66,69,70]

Factors found to be significantly associated with SEH-IVH by univariate analysis were respiratory distress syndrome, artificial ventilation, hypoxia, high concentration of inspired oxygen, patent ductus arteriosus, exchange transfusion, anemia and thrombocytopenia. Two of the study risk factors i.e. birth asphyxia and hypoglycemia were not found to be associated with SEH-IVH. On multivariate logistic model, only three factors retained their significance independently. These factors included RDS requiring artificial ventilation, exchange transfusion and thrombocytopenia. Of these, the babies on assisted ventilation with RDS carried the highest risk of SEH-IVH closely followed by babies undergoing exchange transfusion and thrombocytopenia. Other risk factors like noxious stimulation during routine care giving maneuvers, tracheal suctioning, rapid infusion of colloid, infusion of hyperosmolar solutions like sodium bicarbonate and coagulation disturbances.[70-75] The pathogenesis of SEH-IVH is complex and multifactorial and influenced by intravascular, vascular and extravascular factors.

The optimum mode of delivery for preterm infants at risk for SEH-IVH is controversial. No consistent advantage has been documented with operative delivery compared with the vaginal route.[76, 77]

Severe forms of SEH-IVH i.e. grade III and grade IV, carry a high mortality and morbidity. In the present study 71.4% of infants with SEH-IVH died whereas only 28.6 were either still admitted or discharged.

None of the infants with grade III and grade IV bleeds survived whereas the mortality for grades I & II was 37.5% and 62.5%respectively. This mortality is very high compared to that reported by Murphy.[78] In his study he categorized the mortality of different grades according to the weight of the preterm infants. Mortality of infants <750gms was12%, 24%, 32% and 45% for grades I-IV respectively whereas for infants between751-1500gms (weight more comparable to our study) it was o%,2%,8%and 22%. This difference can be explained by better neonatal facilities available in the developed countries.

Conclusions

1. Almost 1/5th of the babies between 28-34 weeks gestation developed bleed, a significantly high prevalence. This incidence increased with a decrease in gestational age and weight.
2. RDS with ventilation, exchange transfusion and thrombocytopenia were found to be major risk factors.
3. The peak time of occurrence of bleed was first three days of life with, first 24 hours being the most crucial.
4. Resource availability appears to influence aggressiveness of intervention and survival. Within our constraints, a number of interventions are possible to tackle the issue.
5. Antenatal steroids, careful management of premature deliveries, appropriate post-partum resuscitation, prevention of hypoxia and hypoglycemia, avoidance of hypertonic solutions like sodium bicarbonate, adequate control of seizures and gentle handling of small preterm babies are some of the factors easily applicable in all places caring for such infants.

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