

Original Research Article

Intraventricular hemorrhage on mortality and neurological outcomes in premature infants

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ABSTRACT

Background: Intraventricular hemorrhage (IVH) is the commonly encountered clinical event in preterm neonates which imposes significant morbidity and mortality. Although there is a rapid advancement in the neonatal care, IVH is the common cause of neonatal intensive care units admissions. The present study was carried out to evaluate the risk factors, mortality and neurological outcomes in preterm neonates with IVH.

Methods: This was a prospective study conducted on 75 preterm neonates who were delivered before 37 weeks of gestation. The neonates were subjected to cranial ultrasound for the diagnosis of IVH and graded as per the severity. The neonatal and prenatal variables were recorded and analysed to find its association with IVH progression and mortality. Immediate neurological outcome was also assessed among the IVH preterm neonates.

Results: In this study out of 75 preterm neonates, the prevalence of IVH was 18 (24%). The main neonatal factors for IVH are less gestational age at delivery, 28-31 weeks ($p=0.001$), birth weight <1500 gm ($p=0.001$), APGAR scores <5 at 1 and 5 minutes ($p>0.05$) and maternal factors associated with IVH is premature rupture of membranes ($p=0.01$). The mortality rate among the IVH preterm neonates was 7 (38.9%). The significant predictors of mortality were male gender ($p=0.004$), grade III and IV IVH ($p=0.001$) and birth weight ($p=0.001$). The main neurological outcomes observed were seizures and post-hemorrhagic ventricular dilatation.

Conclusions: Increased severity of IVH, early gestational age and low birth weight were associated with mortality in preterm neonates with IVH.

Keywords: IVH, Preterm neonates, IVH severity, Early gestational age, Low birth weight

INTRODUCTION

Intraventricular haemorrhage (IVH) is a most common complication in preterm infants delivered before 32 weeks of gestational age (very or extremely preterm) or with low birth weight less than 2500 grams.¹ Mounting evidence has indicated a 10-20% occurrence of IVH in preterm infants born before the 30th week of gestation and 20-25% among very low birth weight infants.² The IVH severity can increase to 35-45%, when the neonatal weight is below 750 gm.³ The severity of IVH is done by Papile grading system in which grade I forms the mildest

and grade IV forms the severe category.⁴ The mild cases of IVH (Grade I and II) do not shown any impairment in long term neurodevelopmental outcomes in neonates delivered at extremely early GA, but severe grade of IVH (III and IV) leads to cognitive impairment like cerebral palsy and intellectual deficits.⁵

The important risk factors of IVH are early GA, low birth weight (<1500 gm), asphyxia, hypoxia, infection, coagulopathies, twins, abruption of placenta, respiratory distress syndrome which requires surfactant treatment, intrauterine infection, disseminated intravascular

coagulation, pneumothorax and mechanical ventilation.⁶ Preterm babies are more prone to IVH risk since the germinal matrix is not completely matured and thus the blood vessels are more susceptible to rupture. However, in some cases of preterm babies the inherent germinal matrix structure render more prone to hemorrhage.⁷

After IVH, the development of hydrocephalus still worsen the condition of premature neonates with an incidence rate of 25-74% and around 15% of the neonates needs cerebrospinal fluid (CSF) diversion.⁸ Neurological outcome has significant relationship with IVH severity, meanwhile birth weight and gestational age elicits only mild association.⁹

In this backdrop, the present study was carried out to evaluate the risk factors, neurological outcome and mortality among the preterm neonates with Intraventricular haemorrhage.

METHODS

This was a prospective study conducted on 75 preterm infants those delivered before 37 completed weeks admitted to the level 2 NICU with CPAP and high flow setup in Apex hospital, Borivali West, Mumbai, between January 2021 to October 2021. All infants were screened by cranial ultrasound within 3 days after birth, then on day 7, and then weekly until discharge. The diagnosis and classification of IVH were based on those of Papile.⁴ Grade I was germinal matrix hemorrhage, grade II was IVH with no evidence of ventricular dilatation, grade III was IVH affecting 50% of the ventricle with ventricular dilatation (more than 97th percentile of ventricular index) and grade IV was intraparenchymal hemorrhage. The study was conducted after getting the institutional ethical committee approval and the informed consent from the parents.

Inclusion criteria

All preterm neonates >36 weeks of gestational age admitted in neonatal ICU of both genders were included.

Exclusion criteria

Preterm infants with congenital or genetic diseases, cranial damage due to congenital cause, died before cranial ultrasound analysis and who were not willing to participate were excluded from the study.

Clinical features consistent with IVH like convulsion, lethargy, irritability, bulged fontanel, recurrent apnea and sudden onset of respiratory distress in a previously well neonate, sudden pallor and bradycardia were observed and recorded. Cranial ultrasound studies were done within 7 days of life in all cases to identify IVH.

The data related to factors associated with the development of IVH such as antenatal care, place, and

mode of delivery were collected. In addition, other relevant details like pregnancy pregnancy-induced hypertension, maternal use of steroids, time of rupture of membranes, gestational age at delivery, Apgar scores, and the need for postnatal resuscitation or endotracheal intubation were also collected.

Statistical analysis

The data analysis was conducted using SPSS statistical software package v 24. The quantitative variables were represented as mean and standard deviation (SD). The qualitative variables were displayed as frequency and percentage (%). The proportions were compared using Chi-square test and the $p < 0.05$ was considered as statistically significant.

RESULTS

In this study 75 preterm neonates were evaluated and the mean gestational age was 31 ± 3 weeks. The mean birth weight of the preterm neonates was 1543.65 ± 334.76 grams and male preponderance was observed with 48 (64%) were males 27 (36%) were females. Majority of the neonates, 57 (76%) were presented to NICU in the first 24 hours of post-natal life, 14 (18.7%) were admitted between 24-72 hours and 4 (5.3%) were admitted between 4-7 days of post-natal life respectively. Regarding mode of delivery, majority of the neonates had delivered by caesarean section 65 (86.7%) and 10 (13.3%) were delivered by vaginal delivery. The results were shown in Table 1.

Table 1: Demographics and clinical characteristic of the preterm neonates, (n=75).

Parameters	Preterm neonates, (n=75) (%)
Gestational age in weeks (mean $\pm$ SD)	31 $\pm$ 3
Birth weight in gm (mean $\pm$ SD)	1543.65 $\pm$ 334.76
Gender	
Males	48 (64)
Females	27 (36)
Time at presentation to NICU	
<24 hours	57 (76)
24-72 hours	14 (18.7)
4-7 days	4 (5.3)
Mode of delivery	
Caesarean section	65 (86.7)
Vaginal delivery	10 (13.3)
Apgar scores at 1 min	
≤ 5	62 (82.7)
>5	13 (17.3)
Apgar scores at 5 min	
≤ 5	38 (50.7)
6-7	26 (34.7)
>7	11 (14.6)

In this study out of 75 preterm neonates, IVH was present in 18 (24%) of neonates. Regarding IVH severity, out of 18 IVH neonates, 9 (50%) had grade I, 4 (22.2%) had grade II, 3 (16.7%) grade III and 2 (11.1%) had grade IV.

Neonatal risk factors associated with IVH among preterm neonates (Table 2). Incidence of IVH higher in neonates delivered in 28-31 weeks of gestation as compared to 32-36 weeks (41.1 vs 9.8%; $p=0.001$). Meanwhile, neonates with APGAR scores ≤ 5 at 1 min had higher incidence of IVH as compared to neonates with APGAR scores >5 at 1 min (25.8% vs 7.7%; $p=0.001$). Meanwhile, neonates with APGAR scores ≤ 5 at 5 min had higher incidence of IVH as compared to neonates with APGAR 6-7 and >7 at 5 min (39.5% vs 7.7% and 9.1%; $p=0.01$). Prenatal risk factors associated with development of IVH (Table 3). Incidence of IVH was lower in mothers with PIH as compared to IVH mothers with no PIH (11.3% vs 54.5%; $p=0.004$). In contrast, incidence of IVH was higher in mothers with PIH as compared to mothers with no PROM (59.1% vs 9.4%; $p=0.01$).

The clinical features associated with IVH among the preterm neonates were shown in Table 4. In this study the clinical features such as convulsions (100%; $p=0.001$), irritability (72.2% vs 8.8% $p=0.01$), pallor (60% vs 10.9%; $p=0.01$) and respiratory support (68.8% vs 11.9%) were significantly associated with IVH.

In this study out 18 preterm neonates with IVH mortality were observed in 7 (38.9%) and 11 (61.1%) neonates survived. Factor associated with mortality in preterm neonates with IVH was shown in Table 5. The important variables associated with neonatal mortality in IVH cases are male gender (50% vs 16.7%; $p=0.004$), birth weight (43.8% vs 0; $p=0.001$) and IVH grade ($p=0.001$).

Neurological outcome among preterm neonates with IVH was shown in Table 6. Major neurological complication among the IVH neonates was seizure in all the cases, followed by post-hemorrhagic ventricular dilatation in 6 (33.3%) of the neonates, CNS infection in 5 (27.8%) and hydrocephalus in 4 (22.2%) of neonates respectively.

Table 2: Neonatal risk factors associated with the development of IVH in preterm neonates.

Variables	IVH, (n=18) (%)	No IVH, (n=57) (%)	Total, (n=75) (%)	P value
Gender				
Male	12 (25)	36 (75)	48 (100)	0.07NS
Female	6 (22.2)	21 (77.8)	27 (100)	
Mode of delivery				
C-section	15 (23.1)	50 (76.9)	65 (100)	0.54 NS
Vaginal delivery	3 (30)	7 (70)	10 (100)	
Gestational age (weeks)				
28-31	14 (41.1)	20 (58.9)	34 (100)	0.001*
32-36	4 (9.8)	37 (90.2)	41 (100)	
Birth weight (gm)				
500-1499	16 (39)	25 (61)	41	0.01*
1500-2500	2 (5.9)	32 (94.1)	34	
Apgar score at 1 min				
≤5	16 (25.8)	46 (74.2)	62 (100)	0.001*
>5	1 (7.7)	12 (92.3)	13 (100)	
Apgar scores at 5 min				
≤5	15 (39.5)	23 (60.5)	38 (100)	0.01*
6-7	2 (7.7)	24 (92.3)	26 (100)	
>7	1 (9.1)	10 (90.9)	11 (100)	

The association between IVH and no IVH was done using Chi square test. *denotes significant ($p<0.05$), NS- Non significant.

Table 3: Prenatal risk factors associated with the development of IVH in preterm neonates.

Variables	IVH, (n=18) (%)	No IVH, (n=57) (%)	Total, (n=75) (%)	P value
Tocolysis use				
Yes	2 (33.3)	4 (66.7)	6 (100)	0.65
No	16 (23.2)	53 (76.8)	69 (100)	
Pregnancy induced hypertension (PIH)				
Yes	6 (11.3)	47 (88.7)	53 (100)	0.004*
No	12 (54.5)	10 (45.5)	22 (100)	
Premature rupture of membranes (PROM)				
Yes	13 (59.1)	9 (40.9)	22 (100)	0.01*
No	5 (9.4)	48 (90.6)	53 (100)	

The association between IVH and no IVH was done using Chi square test. *denotes significant ($p<0.05$), NS- Non significant.

Table 4: Clinical features associated with IVH among the preterm neonates.

Clinical features	IVH, (n=18) (%)	No IVH, (n=57) (%)	Total, (n=75) (%)	P value
Convulsions				
Yes	12 (100)	0	12 (100)	0.001*
No	6 (9.5)	57 (90.5)	63 (100)	
Irritability				
Yes	13 (72.2)	5 (27.8)	18 (100)	0.01*
No	5 (8.8)	52 (91.2)	57 (100)	
Respiratory distress				
Yes	8 (24.2)	25 (75.8)	33 (100)	0.76NS
No	10 (23.8)	32 (76.2)	42 (100)	
Apnea				
Yes	7 (41.2)	10 (58.8)	17 (100)	0.09NS
No	11 (19)	47 (81)	58 (100)	
Cyanosis				
Yes	2 (10.5)	17 (89.5)	19 (100)	0.52NS
No	16 (28.6)	40 (71.4)	56 (100)	
Pallor				
Yes	12 (60)	8 (40)	20 (100)	0.01*
No	6 (10.9)	49 (89.1)	55 (100)	
Respiratory support				
Yes	11 (68.8)	5 (31.2)	16 (100)	0.001*
No	7 (11.9)	52 (88.1)	59 (100)	

Association between IVH and no IVH was done using Chi square test. *denotes significant ($p < 0.05$), NS- Non significant.

Table 5: Factors associated with the mortality among the IVH preterm neonates.

Variables	Mortality, n (%)		Total, (n=18) (%)	P value
	Died, (n=7)	Survived, (n=11)		
Gender				
Male	6 (50)	6 (50)	12 (100)	0.004
Female	1 (16.7)	5 (83.3)	6 (100)	
Mode of delivery				
Caesarean section	6 (40)	9 (60)	15 (100)	0.08 NS
Vaginal delivery	1 (33.3)	2 (66.7)	3 (100)	
Gestational age				
28-31 weeks	5 (35.7)	9 (64.3)	14	0.09NS
32-36 weeks	2 (50)	2 (50)	4	
Birth weight (gm)				
500-1499	7 (43.8)	9 (56.2)	16	0.001*
1500-2500	0 (0)	2 (100)	2	
Apgar score at 1 min				
≤5	6 (40)	9 (60)	15	0.08 NS
>5	1 (33.3)	2 (66.7)	3	
IVH grade				
I	1 (11.1)	8 (88.9)	9 (100)	0.001*
II	1 (25)	3 (75)	4 (100)	
III	3 (100)	0	3 (100)	
IV	2 (100)	0	2 (100)	

Association between IVH and no IVH was done using Chi square test. *denotes significant ($p < 0.05$), NS- Non significant.

Table 6: Neurological complications among the IVH preterm neonates.

Neurological outcome	Premature neonates with IVH. (n=18) (%)
CNS infection	5 (27.8)
Seizure	18 (100)
Hydrocephalus	4 (22.2)
Posthemorrhagic ventricular dilatation	6 (33.3)
Periventricular Leukomalacia	3 (16.7)

DISCUSSION

IVH is the most commonly encountered clinical condition in premature neonates and it is one of the cardinal etiological factors for brain damage and impaired neurodevelopment outcomes among the neonates. Recently there has been a substantial improvement in the neonatal care and this reduced the mortality rate of preterm neonates when delivered at gestational age less than 25 weeks.¹⁰ Albeit, the incidence of IVH in preterm neonates is ranged between 25-36% and it increases with decrease in gestational age and birth weight.^{11,12} The main risk involved in the development of IVH is the anatomical and physiological features as a result of prematurity.¹³ During prematurity, the germinal matrix is fragile and further lack of muscle and collagen based basement membrane surrounding the large capillaries makes them weak and thus susceptible to IVH.¹⁴ In addition, alterations in the cerebral blood flow, increased cerebral venous pressure and presence of reperfusion injury contributes to the development of IVH in premature neonates.¹⁵ So we aimed to evaluate the risk factors, mortality and neurological outcome in preterm babies with IVH.

The present study was carried out on 75 preterm neonates and prevalence of IVH is 18 (24%). Similarly in a study conducted in India the prevalence of IVH in preterm neonates is 10.8%, in a Bangladesh study the rate is 24.7%, 24.1% in Nigeria and in China study with a high prevalence rate of 42.1%.^{11,16-18}

In the present study majority of the neonates had grade I IVH encompassing 50%. The diagnosis and grading of IVH was done by cranial ultrasound and it is one of the reliable methods for the IVH detection and with good accuracy rate.¹⁹ Likewise in a study done by Motlagh et al among the IVH neonates majority of them had grade I constituting 63.75% and in another study conducted by Wang et al majority of neonates, 35.2% showed grade I IVH.^{11,20}

Wide range of neonatal risk factors is associated with the development of IVH. In our study, the frequency of neonates with IVH is higher in gestational age between 28-31 weeks with 41.1%. Likewise in a study done by Egwu et al logistic regression analysis reveals that neonates born during gestational age <32 weeks had greater odds for the development of IVH and it was significant ($p=0.006$).²¹ The incidence of IVH is higher in neonates born with weight <1500 gm with a rate of 39% as compared to neonates born with weight >1500 gm with 5.9% and it was significant ($p=0.01$). Likewise in a study done by Tadasa et al the odds of IVH were higher in neonates with birth weight <1500g (Adjusted Odds ratio (OR): 0.38; $p=0.03$) as compared to neonates with birth weight >1500 g (16.3% vs 10.7%).²² The incidence of IVH was higher in neonates with APGAR scores <5 at 1 min (25.8%) and 5 mins (39.5%) and it was significant ($p<0.05$). Likewise in a study done by Zhao et al 5-

minute Apgar score <7 displayed significant association with the development of IVH with an OR of 2.273 ($p=0.01$).²³

In the present study the important maternal risk factors associated with the development of IVH is PROM. The incidence of IVH in PROM neonates is 54.5% and, in a study, done by Alyson et al the neonates with PROM born between 23 and 26 of gestation had higher incidence of IVH (4.3%, $p<0.001$).²⁴ Meanwhile, the incidence of IVH was lower in neonates delivered by PIH mothers as compared to non-PIH neonates (11.3% vs 54.5%; $p=0.004$). Previous studies shows that PIH is a reducing factor for IVH in preterm neonates and in a study done by Kashaki et al the incidence of IVH is lower in preeclampsia mothers as compared with no preeclampsia as well as it was significant (16.07% vs 29.05%; $p=0.02$).²⁵

In our study the most significant clinical features among the IVH neonates are convulsion, pallor and irritability. In a study done by Spagnoli et al the most common symptom in IVH neonates is the seizure and majority of the neonates have focal onset and generalized seizure and in addition irritability and respiratory distress syndrome is also encountered in most of the babies.²⁶

In the present study, the prevalence of mortality among the IVH neonates is 7 (38.9%) and in a study done by Adegoke et al the mortality is around 42.7% which is slightly higher as compared to our study and it might be due to the resource-poor setting.¹⁸ In our study the main predictors of mortality in IVH neonates are male gender ($p=0.004$), birth weight ($p=0.001$) and increased IVH severity grades ($p=0.001$). In Tioseco et al study the mortality rate was higher in male neonates as compared to female counterparts (19.8% vs. 3.9%, $p<0.0001$).²⁷ We have observed that neonates with IVH grade III and IV had higher mortality rate than with less severity. Likewise in a study done by Piccolo et al neonates with IVH grade 3 and 4 displayed significant association with mortality with a substantial increase in odds ratio from 6.822 to 19.584 respectively.²⁸ In another study done by Wang et al preterm infants with grade III-IV IVH showed increased mortality and it was significant.¹¹ The reason for mortality in IVH grade III and IV severity is might be due to post-hemorrhagic hydrocephalus which leads to progression of neurological disability and death.²⁹

In this study the most profound neurological outcome was seizure in all the neonates followed by post-hemorrhagic ventricular dilatation, hydrocephalus and CNS infection. Likewise in Piccolo et al study the most common neurological morbidity was convulsion and hydrocephalus.²⁸

Limitations

The present study was limited by, small sample size and utilization of only a single centre.

CONCLUSION

The prevalence of IVH among the preterm neonates in the present study was found to be 24% which is very low when compared to resource poor settings. Low birth weight, low gestational age at delivery and APGAR scores <5 at 1 and 5 mins are the important factors for IVH progression in preterm neonates. Increased IVH severity, grade III and IV is significantly associated with neonatal mortality along with male gender and low birth weight <1500 grams. So, early intervention and accurate steps must be taken in neonates with higher IVH grades to prevent morbidity and mortality.

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