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Original Research Article

Correlation Study of Various Factors with Germinal Matrix-Intraventricular Hemorrhage in Preterm Neonates

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Abstract: The objective of this paper was to study various maternal and neonatal factors in relation to germinal matrix hemorrhage in preterm neonates. It was a hospital based observational study. The subjects included 120 preterm neonates with ≤34 weeks gestation with birth weight between 500 gm to 1500 gm admitted in Neonatal Intensive Care Unit of SDMH Hospital. Various maternal and neonatal risk factors associated with Germinal Matrix – Intraventricular Ventricular Hemorrhage like antenatal complications of pregnancy, prenatal steroids, gestational age, birth weight, hypercapnea, Patent Ductus Arteriosus, pneumothorax etc. were recorded. Routine Cranial Ultrasound was performed within 3 to 5 days of life. The normality of factors was checked using Shapiro–Wilks test and it was found non-normal. Hence, the non parametric correlation coefficient was found using Kendall's Tau. The level of significance was taken as 0.05 and 0.01. The significant positive correlation was observed between IVH and various factors like non-institutional deliveries, Mechanical ventilation, hypoglycemia, rapid bicarbonate infusion and hypercapnea. The significant negative correlation was observed with antenatal steroids and number of steroid doses, gestational age, birth weight, APGAR Score at 1 minute and 5 minutes, blood pH and paO2. Early intervention to prevent GM-IVH in preterm newborns include Institutional delivery, antenatal steroid, optimal management of labor and delivery, careful newborn resuscitation, prevention of respiratory distress syndrome, correction of fluctuating cerebral flow velocity in the ventilated premature neonates with RDS, early detection and prevention of mild degrees of hypercapnea, hypoxemia, acidosis and correction of acidosis with slow infusion of sodium bicarbonate. Routine CUS should be performed as a screening test for early detection of IVH in premature neonates.
Keywords: Neonates, Germinal Matrix, Intraventricular hemorrhage

INTRODUCTION

The germinal matrix is gelatinous fine network of blood vessels and primitive neuronal tissue which lie immediately ventrolateral to lateral ventricular system. Due to fragile nature of the involuting vessels of germinal matrix in preterms, these vessels are susceptible to rupture and lead to intraventricular hemorrhage. Germinal matrix Intraventricular Hemorrhage (GM-IVH) is one of the most important neurological complications in premature and Very Low Birth Weight (VLBW) newborns. It is associated with high mortality as well as the possibility of later neuro-developmental sequelae. It is important to detect this entity early [1].

The pathogenesis of GM-IVH in preterm infants is multi-factorial. The maternal risk factors include maternal age, pregnancy induced hypertension, premature rupture of membrane, antepartum hemorrhage, anemia, vaginal route of delivery and non institutional delivery. The neonatal risk factors include gestational age, birth weight, sex, APGAR score, respiratory distress syndrome, ventilator associated asynchrony, patent ductus arteriosus, hypercarbia, birth asphyxia, hypovolemia, hypotension, shock, systemic hypertension, rapid infusion of colloid, normal saline or hyperosmolar solutions, tracheal suctioning, high continuous positive airway pressure, pneumothorax, seizures, anemia, hypoglycemia, obstructed labour, infants requiring cardiopulmonary resuscitation, apnea, sepsis and caretaking procedure[2]. The present study was undertaken to find the incidence of GM-IVH by non-invasive cranial ultra-sonography and various risk factors responsible.

SUBJECTS AND METHODS

It was an observational study conducted on 120 preterm and low birth weight babies admitted in

NICU of Santokba Durlabhji Memorial hospital and research institute over a period of one year, a 350 bedded multi specialty centre at Jaipur. The objective was to determine incidence of GM-IVH and various maternal and neonatal factors responsible. The study included inborn and out born preterm babies (≤34 weeks gestation), birth weight between 500 gm and 1500 gm and those admitted within 24 hours of birth. Babies <23 weeks GA and birth weight <500 and ≥1500 gm were excluded. Babies with congenital malformation except PDA were also excluded.

Maternal details including age, parity, antenatal checkups, antenatal steroids, antenatal complications, and mode of delivery were recorded as per history given by family members, hospital records or records available in case of out born deliveries. Details were recorded in predesigned proforma, which consists of maternal and neonatal profile. Maternal profile included demographics, parity, Booked/Unbooked, medical complications of pregnancy like anemia, Pregnancy Induced Hypertension (PIH), eclampsia, Ante Partum Hemorrhage (APH), premature rupture of membrane, urinary tract infection, preterm delivery, chronic medical diseases (Diabetes, cardiac, pulmonary , renal etc.) and prenatal steroids. Neonatal profile like birth weight, APGAR score at 1 and 5 minutes and resuscitative interventions were recorded. Informed consent was obtained. Routine Cranial Ultrasound (CUS) was performed in all infants born at ≤34 weeks of gestational age within 3 to 5 days of life. In very sick very low birth weight CUS was performed within 24 hours of birth. Findings of CUS scans were classified by system described by Papile *et al.* for CT[3].

STATISTICAL METHODS

The normality of factors was checked using Shapiro–Wilks test and it was found non-normal. Hence, the non parametric correlation coefficient was found using Kendall's Tau. The level of significance was taken as 0.05 and 0.01.

RESULTS

In the present study the incidence of GM- IVH was 15% in preterm neonates. 'The significant positive correlation for occurrence of IVH among maternal risk factors was found more in non-institutional delivery as compared to inborn deliveries (r=0.244,p<0.05) and those with irregular antenatal checkups cases (r=0.358, p<0.01). The significant negative correlation for occurrence of IVH was found with antenatal steroids and number of steroid doses. The usage of antenatal steroids decreased the incidence of IVH (r= -0.210, p<0.05). In the present study, the occurrence of IVH in neonates with maternal complications like anemia (r=0.079, p >0.05), PIH (r=-0.064, p>0.05), APH (r=0.169, p>0.05), PROM (r=0.098, p>0.05) was found to be statistically nonsignificant with IVH. This was due to lesser incidence of antenatal complications among mothers.

The significant positive correlation for occurrence of IVH was more among males as compared to females (r=0.207, p<0.05).The incidence of IVH increases with respiratory distress syndrome in preterm (r=0.355, p<0.01). Mechanical ventilation was significantly associated with IVH (r=0.462, p<0.01). Risk of IVH increased with decrease in blood glucose (r=0.188, p<0.05) and rapid infusion of soda bicarbonate (r=0.398, p<0.01). In our study, the hypercapnea is associated with IVH (r=0.36, p<0.01).The significant negative correlation for IVH was found with gestational age (r= -0.296, p<0.01)., birth weight (r = -0.202, p<0.01), APGAR Score at 1 minute (r= -0.444, p<0.01) and 5 minute (r = -0.461, p<0.01), blood pH(r= -0.404, p<0.01) and paO2(r= -0.346, p<0.01).

In the present study, the occurrence of IVH in neonates with PDA (r=.029, p>0.05) and pneumothorax (r=.128, p>0.05) was not found significantly associated with IVH. This may be due to the limited number of cases of PDA and pneumothorax in our nursery.

Table-1: Baseline Characteristics (Study variables)

Type (n=120)	**No.**	**%**
VLBW	108	90.00
LBW	12	10.00
Male	71	59.16
Female	49	40.80
Inborn (Institutional)	85	70.83
Out born (Non institutional)	35	29.16
Mother booked	76	63.33
Mother unbooked	44	36.67
Vaginal Delivery	63	52.50
LSCS	57	47.50
IVH absent	102	85.00
IVH present	18	15.00
Antenatal care Received	49	44.14
Antenatal care Not Received	62	55.85

Type	**Min.**	**Max.**	**Mean**	**Std. Dev.**
Age	18	34	25.92	2.608
Gestation (wks)	25	34	31.38	2.166
Birth wt. (gms)	600	1490	1260.97	209.908

Table 2: Maternal risk factors

Correlations		
Maternal risk factors		IVH
Inborn = 1	r value	0.244
Out born = 2	P value	0.008
Booked=1	r value	0.358
Unbooked=2	P value	0
Antenatal steroids	r value	-0.21
	P value	0.019
Anemia	r value	0.079
	P value	0.39
PIH	r value	-0.064
	P value	0.484
APH	r value	0.169
	P value	0.065
PROM	r value	0.098
	P value	0.283

Table 3: Neonatal risk factors

Correlations		
Neonatal risk factors		**IVH**
Sex	r value	0.207
	P value	0.024
Gestation (wks)	r value	-0.296
	P value	0.000
Birth wt. (gms)	r value	-0.202
	P value	0.008
APGAR Score at 1 min	r value	-0.444
	P value	0.000
APGAR Score at 5 min	r value	-0.461
	P value	0.000
Respiratory distress	r value	0.355
	P value	0.000
Mechanical Ventilation	r value	0.462
CPAP=I		
IPPV=2	P value	0.000
Hypoglycemia (<40mg/dl)	r value	0.188
	P value	0.040
Infusion of Sodium Bicarbonate	r value	0.398
	P value	0.000
Pneumothorax	r value	0.128
	P value	0.164
PDA	r value	0.029
	P value	0.750
PaCo2	r value	0.360
	P value	0.000
Ph	r value	-0.404
	P value	0.000
PaO2	r value	-0.346
	P value	0.000

DISCUSSION

The significant positive correlation for occurrence of IVH was found with various maternal risk factors .The incidence of IVH was higher in out born delivery as compared to inborn deliveries ($r=0.244$, $p<0.05$). Infants born at level I hospitals and transported later to the higher centers were at risk of developing IVH than the transportation in utero, which have lower incidence of IVH [4]. The occurrence of IVH was more common in unbooked cases ($r=0.358$, $p<0.01$).The significant negative correlation for occurrence of IVH was found with antenatal steroids and number of doses of steroids. The antenatal steroids had decreased the incidence of IVH ($r= -0.210$, $p<0.05$).The incidence of IVH was less in neonates whose mothers received complete doses of steroids antenatal ($r= -0.201$, $p<0.05$).

The antenatal administration of glucocorticoid decreases the incidence of RDS and IVH [5]. The antenatal steroids decrease the need for blood pressure support and lessen hypotension postnatally, thus improving cardiovascular stability in infants who were treated [6]. In a study incidence of GM-IVH was twofold to three fold lower in infants whose mothers received a complete course of steroids antenatally compared to infants whose mothers received no steroids or an incomplete course [7]. The possibility also exists that therapy leads to beneficial effect in part by stimulation of maturation of brain structures (e.g. germinal matrix) [8].

Among neonatal factors significant positive correlation of IVH was found with gender, respiratory distress syndrome, mechanical ventilation, hypoglycemia, rapid infusion of sodium bicarbonate and hypercapnea. The IVH was more among males as compared to females ($r=0.207$, $p<0.05$). The few studies also correlated male sex with increased incidence of IVH [9, 10]. The incidence of IVH increased with respiratory distress syndrome in preterm ($r=0.355$, $p<0.01$). In the preterm infants with RDS, continuous fluctuations of blood flow in the vulnerable germinal matrix micro vessels occur which may be possible reason for the development of IVH [11].

In the study, mechanical ventilation was significantly associated with IVH ($r=0.462$, $p<0.01$). The ventilated preterm infants with RDS, whose breaths are not synchronized with the ventilator, beat to beat fluctuations in blood pressure may occur, resulting in fluctuations in cerebral perfusion and subsequently may cause IVH [11].

Risk of IVH also increased with decrease in blood glucose ($r=0.188$, $p<0.05$). Decline in the level of blood glucose alters the cerebral blood flow, leading to IVH [12, 13]. The rapid infusion of sodium bicarbonate was also associated with IVH ($r=0.398$, $p<0.01$). Earlier studies also reported that the rapid infusion of hyperosmolar sodium bicarbonate was associated with significant increase in the incidence of IVH [1, 4, 14].

One study found that the administration of sodium bicarbonate after the first day of life was a significant risk factor[15]. Rapid infusion of sodium bicarbonate relate in part to abrupt elevation of $PaCO_2$ that result in poor ventilated or non-ventilated patient from the buffering effect of bicarbonate [1]. The elevated $PaCO_2$ then acts on cerebral arterioles leading to increase cerebral perfusion, followed by rupture of these vessels. In our study, the hypercapnea is associated with IVH ($r=0.36$, $p<0.01$). The few studies also showed strong association of hypercapnea with IVH which was similar to our study [1, 4, 5, 16, 17, 18]. There is a pronounced change in cerebral blood flow to changes in $PaCO_2$ which may be responsible for IVH [19].The significant negative correlation for IVH was found with gestational age, birth weight, APGAR score at 1 minute and 5 minute, pH and paO2.

The incidence of IVH decreased with increase in gestational age ($r=-0.296$, $p<0.01$).The GM- IVH originates in the subependymal germinal matrix layer of developing brain. The germinal matrix is highly vascular layer, most pronounced in the fetus of 24 to 32 weeks of gestation. This layer gradually decreases in size as fetus matures and virtually disappears by term. [1] The risk of IVH was lesser in babies with normal birth weight ($r= -0.202$, $p<0.01$). The frequency of IVH is inversely related to the birth weight of the neonate [5, 18, 20].

Asphyxia is in relation with low APGAR score at 1 and 5 minutes and requiring cardiopulmonary resuscitation was an important factor. Neonates with IVH had significantly low APGAR score at 1 minute ($r= -0.444$, $p<0.01$) and 5 minutes ($r= -0.461$, $p<0.01$) as reported. The previous studies also found that low APGAR score had association with IVH. [5,9,16-18,21] One study had demonstrated that Perinatal asphyxia may be associated with increase in cerebral blood flow with impaired vascular auto regulation, increase in cerebral venous pressure, decrease in cerebral blood flow associated with hypotension and may result in injury to matrix capillaries [19].

In the present study, hypoxemia was significantly associated with IVH ($r=-0.346$, $p<0.01$). The hypoxemia result in cerebral vasodilatation and if sustained, lead to loss of the protective, cerebral auto regulatory mechanism. Thus, cerebral blood flow may become pressure-passive with direct transmission of systemic pressure to cerebral vasculature leading to IVH [19].

In the present study, acidosis was significantly associated with the IVH ($r= -0.404$, $p<0.01$). Few studies had similar results. [1, 4, 19,22]. The cerebral blood flow changes with change in pH. The acidosis impairs cerebral auto regulatory mechanism. Thus, any change in intravascular pressure can be transmitted to unprotected micro vessels leading to IVH [19].

CONCLUSION

The risk factors significantly associated with the IVH included obstetric and neonatal factors. Obstetric factors were unbooked case and lack of exposure of steroids to mothers during antenatal period. Neonatal factors were low gestational age, low birth weight, male sex, out born deliveries, low APGAR score at 1 and 5 minutes, hypoglycemia, RDS, hypercapnea, mechanical ventilation, acidosis, hypoxemia and infusion of sodium bicarbonate. Timely interventions and proper antenatal care may save these babies from IVH leading to sequelae later in life.

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