Original Article

Risk and Prognostic Factors in Perinatal Hemorrhagic Stroke

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Abstract

Background: Perinatal stroke encompasses a heterogeneous group of focal neurological injuries early in brain development. In this study, we aimed to compare risk and prognostic factors in preterm and term infants with perinatal hemorrhagic stroke (PHS). **Patients and Methods:** The study includes 66 infants with PHS. The infants were evaluated for demographic characteristics, fetal and maternal risk factors, perinatal events, clinical and neuroimaging findings, complications, and sequales. **Results:** Of 66 infants with PHS, 44 (66.70%) were preterm and 22 (33.30%) were term infants. Primiparity, mucosal bleeding, and multiple lobes involvement were more common in term infants than preterm infants ($P < 0.05$); however, respiratory insufficiency, neonatal sepsis, perinatal asphyxia, respiratory distress syndrome, use of invasive mechanical ventilation, use of noninvasive mechanical ventilation, and prolonged hospitalization were more common in preterm infants than term infants ($P < 0.05$). Eight (12.12%) infants died during infancy period. Small for gestational age and mucosal bleeding were more common in infants who are dead than those alive ($P < 0.05$). Forty-two (63.63%) infants were followed. Cerebral palsy and/or epilepsy and/or hydrocephalus were diagnosed in 36 (85.72%) infants during follow-up. **Conclusion:** Our findings showed that PHS was much more common in preterm infants. Mucosal bleeding and multiple lobes involvement were more common in term infants. PHS has high morbidity and mortality rates. Small for gestational age and mucosal bleeding were more common in infants who are dead.

Keywords: Hemorrhage, infant, perinatal stroke

Introduction

Perinatal stroke is defined as an acute neurologic syndrome due to cerebral injury of vascular origin occurring between 20 weeks gestation and 28 days postnatal life. It probably affects more than 5 million people worldwide.[1,2] Perinatal stroke includes both ischemic and hemorrhagic events resulting from disruption of either arteries or veins from early gestation through the first month of life.[1,2] It is a common cause of acute neonatal encephalopathy, and may manifest as seizures, altered mental status, abnormalities of muscular tone, and sensorimotor deficits.[2-4]

Perinatal hemorrhagic stroke (PHS) including germinal matrix hemorrhage (GMH) and intraventricular hemorrhage (IVH) is most probably of multifactorial origin and can occur not only in the postnatal but also in the antenatal and perinatal period.[5] Multiple risk factors in the antenatal and perinatal period have been and are still being identified for GMH-IVH as follows: Infection and inflammation, coagulation profile, mode of delivery, site of delivery, delayed cord clamping, resuscitation, cardiovascular factors, respiratory factors, electrolyte disturbances, and genetic factors.[5] There are currently no strategies that decrease the risk of perinatal stroke.[6] Overall, outcomes from perinatal stroke are poor, with most patients developing lifelong neurological disabilities including cerebral palsy (CP), epilepsy, and cognitive, language, and behavioral challenges.[1,7]

In this article, we evaluated clinical and laboratory findings of infants with PHS to compare risk and prognostic factors in preterm and term infants with PHS.

Patients and Methods

The study includes 66 infants with PHS admitted to a tertiary referral university hospital, Medical Faculty, Department of Neonatology between January 2011 and May 2018. PHS was defined as imaging evidence of blood within the brain parenchyma with or without intraventricular or subarachnoid blood.[8] The patients' data were obtained from chart review of hospital records. First, the records of all those diagnosed with perinatal stroke were reviewed from hospital database and then infants with incomplete data were excluded. Infants with definite PHS were identified and their data on Departments of Neonatology and Pediatric Neurology were reviewed, retrospectively. Infants with perinatal arterial ischemic stroke, cerebral sinovenous thrombosis, periventricular venous infarction, and presumed perinatal stroke were excluded.

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Hemorrhagic transformation of arterial ischemic stroke or cerebral sinovenous thrombosis and cases where blood was exclusively extra-axial were also not included in the study. The infants were evaluated for demographic characteristics, fetal and maternal risk factors, perinatal events, clinical and neurological findings, early and late complications, sequales, and neuroimaging findings including transfontanelle ultrasonography (US), cranial computerized tomography (CT), and cranial magnetic resonance imaging (MRI).

In our neonatology department, transfontanelle US is routinely performed in all hospitalized preterm infants within 3 days of admission and once a week during their follow-up until discharge and in all term infants within 3 days of admission and just before discharge from hospital. Transfontanelle US was performed by a neonatologist, H.A. by using M2540A Diagnostic Ultrasound Imaging System, Philips, Bothell, WA, USA. Examinations of cranial MRI (T1-weighted, T2-weighted, diffusion-weighted imaging and apparent diffusion coefficient mapping, fluid attenuated inversion recovery-weighted axial and sagittal sections) by using 1.5 Tesla Siemens Magnetom Symphony (Siemens, Erlangen, Germany) and cranial CT by using Siemens Somatom Sensation 64 (Siemens, Erlangen, Germany) were performed at Medical Faculty, Department of Radiology. Both cranial MRI and CT findings were evaluated by a radiologist, S.A. In order to detect etiological factors or accompanying disorders, hematological, biochemical, microbiological, and thrombophilia panel tests and echocardiogram were performed in required infants.

On statistical analysis, descriptive statistics were given as mean and standard deviation or median, Q1 and Q3 for continuous variables where appropriate. Frequency and percentages of categorical variables were given. T test or Mann–Whitney *U* test was used when comparing continuous outcomes. Chi-square or Fisher's exact test was used to compare categorical variables among groups. All analyses were performed using SAS University Edition 9.4 software. A *P* value of <0.05 was considered significant.

The study was approved by the ethical committee of Medical Faculty (Decision number: 2018/1245; Date of the approval: 02 March 2018).

Results

Demographic, clinical, and laboratory characteristics, risk factors, and outcomes in preterm and term infants with PHS are mentioned in Table 1. PHS was much more common in preterm infants than term infants. Diagnosed congenital heart defects (CHD) were as follows: Secundum type atrial septal defect in four infants; patent foramen ovale in three; patent ductus arteriosus in three; ventricular septal defect in two; atrial septal defect and ventricular septal defect in two; truncus arteriosus in one; tetralogy of Fallot in one; and atrial septal defect, ventricular septal defect, and patent ductus arteriosus in one infant. Detected bleeding diatheses were as follows: Thrombocytopenia in six, factor VII deficiency in two, and factor X deficiency in one infant. Hemorrhage was due to a venous malformation on left hemisphere in another infant. Primiparity, mucosal (nose and/or mouth) bleeding, and multiple lobes involvement were more common in term infants than preterm infants ($P < 0.05$); however, respiratory insufficiency, neonatal sepsis, perinatal asphyxia, respiratory distress syndrome, use of invasive mechanical ventilation, use of noninvasive mechanical ventilation, and prolonged hospitalization were more common in preterm infants than term infants ($P < 0.05$). No statistically significant difference was found between preterm and term infants for other characteristics ($P > 0.05$).

Transfontanelle US was performed in all infants. Cranial MRI and CT examinations were performed in 46 and seven infants, respectively, and both of them were performed in 13 infants [Figure 1]. In addition to intra-axial hemorrhage, extra-axial hemorrhage was diagnosed in 25 (37.87%) infants as follows: Subdural hemorrhage in 15 infants, subarachnoid hemorrhage in six, subgaleal hemorrhage in two, and subcutaneous hemorrhage in two infants. None of the infants required evacuation of hematomas; however, ventriculoperitoneal shunt was placed in eight infants because of hydrocephalus.

Of 66 infants with PHS, 42 (63.63%) infants were followed for 20.52 ± 30.23 months (between 1 and 68 months) [Table 1]. We did not find a statistically significant difference between preterm and term infants for outcomes ($P > 0.05$). Of 32 infants with hydrocephalus, four (12.50%) infants died and six (18.75%) infants had no follow-up. Of the remaining 22 infants with hydrocephalus, 18 infants had cerebral palsy and/or epilepsy and four infants showed normal neurological development.

Demographic, clinical, and laboratory characteristics and risk factors in infants who are dead and those alive in PHS are shown in Table 2. Nine (13.63%) infants died. Eight (12.12%) infants died during infancy period due to following causes: Five infants from sepsis and respiratory failure and one each infant died due to sepsis and subarachnoid hemorrhage, sepsis and acute lymphoblastic leukemia, and heart failure due to truncus arteriosus. Follow-up period of these eight infants were 36.25 ± 28.28 days. The remaining infant with ventriculoperitoneal shunt due to hydrocephalus died due to sepsis after ileostomia operation at 4 years of age. We did not include this infant in Table 2, because he died after infancy period. We found that small for gestational age as a risk factor for PHS and mucosal bleeding were more common in infants who are dead than those alive ($P < 0.05$). No statistically significant difference was found between two groups for other characteristics ($P > 0.05$).

Discussion

This study showed that nine (13.63%) infants had bleeding diathesis including thrombocytopenia, factor VII and X deficiencies, and an infant had venous malformation. In

Table 1: Demographic, clinical, and laboratory characteristics and outcomes in preterm and term infants with perinatal hemorrhagic stroke

Characteristics and risk factors	Preterm infants *N*=44 *n* (%)	Term infants *N*=22 *n* (%)	*P*
Gender			1.000
Male	32 (72.73)	16 (72.73)	
Female	12 (27.27)	6 (27.27)	
Twin pregnancy	3 (6.82)	0 (0.00)	0.545
Oligohydramnios	6 (13.64)	4 (18.18)	0.720
Risk factors			
Maternal age (year) (mean±SD)	29.70±5.53	26.68±7.14	0.091
Gestational age (week) (mean±SD)	30.56±3.36	37.86±0.99	<0.001
Birth weight (kg) (mean±SD)	1.51±0.60	2.90±0.60	<0.001
Caesarean section	37 (84.09)	14 (63.64)	0.061
Chorioamnionitis	16 (36.36)	3 (13.64)	0.055
Small for gestational age	15 (34.09)	4 (18.18)	0.277
Primiparity	9 (20.45)	10 (45.45)	0.034
Preterm premature rupture of membranes	5 (11.36)	0 (0.00)	0.160
Perinatal asphyxia	34 (77.27)	10 (45.45)	0.009
Neonatal sepsis	35 (79.55)	12 (54.55)	0.034
Respiratory distress syndrome	31 (70.45)	8 (36.36)	0.008
Congenital heart defect	14 (31.81)	3 (13.64)	0.111
Bleeding diathesis	3 (6.82)	6 (27.27)	0.050
Necrotizing enterocolitis	4 (9.09)	1 (4.55)	0.657
Comorbid states			
Hydrocephalus	22 (50)	10 (45.45)	0.728
Hypoglycemia	2 (4.55)	0 (0.00)	0.548
Maternal urinary tract infection	2 (4.55)	0 (0.00)	0.548
Symptoms			
Respiratory insufficiency	36 (81.82)	10 (45.45)	0.002
Convulsion	12 (27.27)	6 (27.27)	1.000
Feeding intolerance	8 (18.18)	7 (31.82)	0.212
Hypotonia/hypertonia	3 (6.82)	3 (13.63)	0.392
Mucosal bleeding	0 (0.00)	3 (13.63)	0.033
Brain regions involved			0.034
Single lobe	8 (18.8)	3 (13.64)	
Multiple lobes (2 or more)	7 (15.91)	10 (45.45)	
Others (intraventricular, germinal matrix, and choroid plexus)	29 (65.91)	9 (40.91)	
Lateralization of hemorrhage			1.000
Bilateral	33 (75.00)	16 (72.73)	
Right	7 (15.91)	4 (18.18)	
Left	4 (9.09)	2 (9.09)	
Localization of hemorrhage			0.163
Single localization of hemorrhage	18 (40.91)	13 (59.09)	
Brain parenchyma	7 (15.91)	8 (36.36)	
Intraventricular	1 (2.27)	2 (9.09)	
Germinal matrix	10 (22.73)	3 (13.64)	
Multiple localization of hemorrhages (2 or more)	26 (59.09)	9 (40.91)	
Germinal matrix + intraventricular	12 (27.27)	2 (9.09)	
Brain parenchyma + intraventricular	4 (9.09)	3 (13.64)	
Germinal matrix + brain parenchyma	1 (2.27)	0 (0.00)	
Germinal matrix + brain parenchyma + intraventricular	3 (6.82)	0 (0.00)	
Germinal matrix + intraventricular + choroid plexus	6 (13.64)	2 (9.09)	
Brain parenchyma + intraventricular + choroid plexus	0 (0.00)	2 (9.09)	
Use of invasive mechanical ventilation	34 (77.27)	11 (50.00)	0.025
Duration of use of invasive mechanical ventilation (median [Q1-Q3]) (day)	8 (5.25-20.0)	6 (3.0-13.5)	0.078

Contd...

Table 1: Contd...

Characteristics and risk factors	Preterm infants *N*=44 *n* (%)	Term infants *N*=22 *n* (%)	*P*
Use of noninvasive mechanical ventilation	37 (84.09)	8 (36.36)	<0.0001
Duration of use of noninvasive mechanical ventilation (median [Q1-Q3]) (day)	5 (3.0-10.0)	4 (2.75-7.0)	0.231
Duration of hospitalization (median [Q1-Q3]) (day)	43.0 (30.0-64.25)	13.5 (6.0-24.25)	<0.001
Outcomes	**Preterm infants *N*=28 *n* (%)**	**Term infants *N*=14 *n* (%)**	***P***
Normal outcome	4 (14.28)	2 (14.29)	1.000
Abnormal neurologic outcome	24 (85.72)	12 (85.71)	
Cerebral palsy	6 (21.43)	4 (26.66)	
Hydrocephalus	2 (7.14)	2 (13.33)	
Epilepsy	1 (3.57)	2 (13.33)	
Cerebral palsy + hydrocephalus	7 (25.00)	1 (6.67)	
Cerebral palsy + epilepsy	1 (3.57)	0 (0.00)	
Epilepsy + hydrocephalus	2 (7.14)	1 (6.67)	
Cerebral palsy + epilepsy + hydrocephalus	5 (17.85)	2 (13.33)	

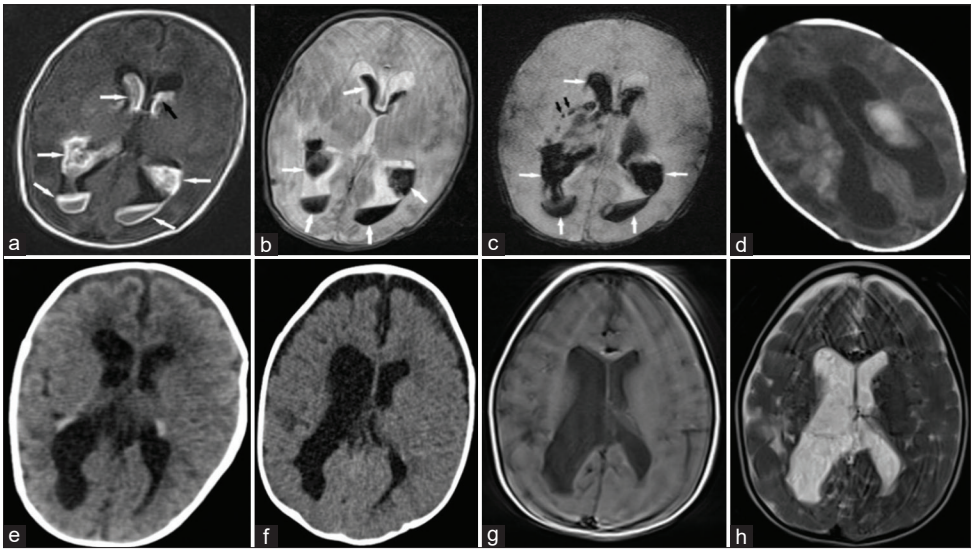

Figure 1: In a preterm girl on day 12 of life, T1-weighted imaging shows hyperintensity in left ganglionic eminence (black arrow), and ventricles (white arrows) (a). T2-weighted imaging shows hypointense (white arrows) (b). Susceptibility-weighted imaging shows hemorrhages in periventricular (black arrows) and lateral ventricles (white arrows) (c). Computerized tomography shows ventriculomegaly (d, at 20 days old; e, at 2 months old; f, at 8 months old). At 2-year and 6-month old, magnetic resonance imaging shows ventriculomegaly and periventricular volume loss (g, T1-weighted; h, T2-weighted)

the series of Armstrong-Wells *et al*.[9] including 20 cases of PHS (19 intracerebral hemorrhage [ICH] and one subarachnoid hemorrhage), etiologies included thrombocytopenia ($n = 4$) and cavernous malformation ($n = 1$); 15 (75%) were idiopathic. In another series, hemostatic abnormalities were noted in 38% infants with PHS.[10] Causes of PHS in our infants were similar to those of literature.

In our study, all infants had one or more risk factors for PHS; prematurity, cesarean section, perinatal asphyxia, neonatal sepsis, and respiratory distress syndrome were the most common risk factors for PHS. Bruno *et al*.[10] noted that major risk factors in infants with PHS included CHD (26%) and fetal distress (21%). In a series including 86 infants with PHS, idiopathic PHS was independently associated with lower maternal age, primiparity, prior spontaneous abortion, difficult fetal transition, and small for gestational age.[8] Hong and Lee[11] noted traumatic delivery in 20 (47.6%), and perinatal asphyxia in 21 (50.0%) patients after reviewing of 42 neonates with ICH. Armstrong-Wells *et al*.[9] noted that multivariate predictors of PHS included fetal distress and postmaturity. Lu *et al*.[12] reported that lower gestational age, low birth weight, asphyxia resuscitation, and maternal chorioamnionitis were independent risk factors for IVH in preterm infants born at 34 weeks of gestation or less following preterm premature rupture of membranes. Risk factors diagnosed in our cases were mostly compatible with the literature. In our study, CHD was present in one-quarter of the cohort. However, none of the infants with CHD underwent cardiac surgery and had cerebral sinovenous thrombosis. Claessens *et al*.[13] noted that all neonates with

Table 2: Demographic, clinical, and laboratory characteristics and risk factors in infants who are dead and those alive in perinatal hemorrhagic stroke

Characteristics and risk factors	Infants who are alive *N*=58 *n* (%)	Infants who are dead *N*=8 *n* (%)	*P*
Gender			0.488
Male	43 (74.14)	5 (62.50)	
Female	15 (25.86)	3 (37.50)	
Twin pregnancy	3 (5.17)	0 (0.00)	1.000
Oligohydramnios	9 (15.52)	1 (12.50)	1.000
Risk factors			
Maternal age (year) (mean±SD)	28.69±6.16	28.75±7.12	0.982
Gestational age (week) (mean±SD)	32.98±4.41	33.13±4.99	0.941
Birth weight (kg) (mean±SD)	2.02±0.90	1.66±0.76	0.254
Cesarean section	44 (75.86)	7 (87.50)	0.670
Prematurity	39 (67.24)	5 (62.50)	1.000
Chorioamnionitis	15 (25.86)	4 (50.00)	0.213
Small for gestational age	14 (24.14)	5 (62.50)	0.038
Primiparity	17 (29.31)	2 (25.00)	1.000
Preterm premature rupture of membranes	5 (8.62)	0 (0.00)	1.000
Perinatal asphyxia	38 (65.52)	6 (75.00)	0.708
Neonatal sepsis	39 (67.24)	8 (100.00)	0.093
Respiratory distress syndrome	33 (56.90)	6 (75.00)	0.455
Congenital heart disorder	13 (22.41)	4 (50.00)	0.088
Bleeding diathesis	7 (12.07)	2 (25.00)	0.298
Necrotizing enterocolitis	4 (6.90)	1 (12.50)	0.487
Comorbid states			
Hydrocephalus	28 (48.27)	3 (37.50)	0.567
Hypoglycemia	2 (3.45)	0 (0.00)	1.000
Maternal urinary tract infection	2 (3.45)	0 (0.00)	1.000
Symptoms			
Respiratory insufficiency	41 (70.69)	5 (62.50)	0.690
Convulsion	17 (29.31)	1 (12.5)	0.429
Feeding intolerance	14 (24.14)	1 (12.5)	0.670
Hypotonia/hypertonia	5 (8.62)	1 (12.5)	0.554
Mucosal bleeding	1 (1.72)	2 (25.00)	0.036
Lateralization of hemorrhage			0.431
Bilateral	42 (72.41)	7 (87.50)	
Right	11 (18.97)	0 (0.00)	
Left	5 (8.62)	1 (12.50)	
Brain regions involved			0.325
Single lobe	10 (17.24)	1 (12.50)	
Multiple lobes (2 or more)	13 (22.41)	4 (50.00)	
Others (intraventricular, germinal matrix, and choroid plexus)	35 (60.35)	3 (37.50)	
Localization of hemorrhage			0.922
Multiple localization (2 or more)	31 (53.45)	4 (50.00)	
Single localization of hemorrhage	27 (46.55)	4 (50.00)	
Brain parenchyma	13 (22.41)	2 (25.00)	
Intraventricular	3 (5.17)	0 (0.00)	
Germinal matrix	11 (18.97)	2 (25.00)	
Use of invasive mechanical ventilation	38 (65.52)	7 (87.50)	0.419
Duration of use of invasive mechanical ventilation (median [Q1-Q3]) (day)	7.50 (5.00-15.00)	16 (9.50-24.50)	0.311
Use of noninvasive mechanical ventilation	42 (72.41)	3 (37.50)	0.098
Duration of use of noninvasive mechanical ventilation (median [Q1-Q3]) (day)	5 (2.25-8.00)	10 (7.50-25.00)	0.374
Duration of hospitalization (median [Q1-Q3]) (day)	32.50 (14.00-51.50)	17.50 (15.00-33.75)	0.974

critical CHD are exposed to the cardiopulmonary bypass circuit in early life, and this in itself might be a risk factor for the development of cerebral sinovenous thrombosis.

The symptoms on admission were respiratory insufficiency, convulsion, feeding intolerance, hypotonia/hypertonia, and mucosal bleeding in our study. Common presentations in PHS included seizure, apnea, and poor feeding or vomiting.[10] In a series including 86 infants with PHS, most presented in the first week of life with seizures and encephalopathy.[8] Cases were presented with encephalopathy (100%) and seizures (65%) in 20 cases of PHS.[10] In the series of Hong and Lee,[11] seizure or seizure-like activity was the most common presenting symptom (40.5%), with apnea seen in another seven infants (16.7%). Brouwer *et al*.[14] reviewed 53 term infants with ICH with parenchymal involvement. Seizures were the most common presenting symptom (71.7%), another 10 (18.9%) infants presented with apneic seizures, and five infants had no clinical signs but were admitted to neonatal intensive care unit because of perinatal asphyxia ($n = 2$), respiratory distress ($n = 2$), and development of posthemorrhagic ventricular dilatation ($n = 1$).[14] Main clinical findings were seizures, abnormalities of muscular tone (hypotonia/hypertonia), and disturbed level of alertness in another series with perinatal stroke.[3] Contrary to the literature, three infants were presented with mucosal bleeding in our series.

Our study showed that PHS was much more common in preterm infants than term infants (22 versus 44). Primiparity and mucosal bleeding were more common in term infants than preterm infants ($P < 0.05$); however, respiratory insufficiency, neonatal sepsis, perinatal asphyxia, and respiratory distress syndrome were found more common in preterm infants than term infants ($P < 0.05$). Bruno *et al*.[10] reviewed 42 term and late preterm neonates with hemorrhagic stroke (median gestational age was 39.7 weeks; interquartile range 38–40.7 weeks); however, they did not compare findings of term and late preterm neonates. Lee *et al*.[15] compared 10 infants with perinatal arterial ischemic stroke and 20 infants (six were late preterm) with PHS, but term and late preterm infants with PHS were not compared. This is the first cohort study about comparison of preterm and term infants with PHS. The difference between the preterm and term infants regarding the perinatal complications is well known. However, why primiparity and mucosal bleeding were more in term infants? We could not explain the reason for these important findings.

In our series, brain parenchyma, germinal matrix, intraventricular, and choroid plexus hemorrhages were diagnosed in both preterm and term infants. GMH was noted in 32 (48.48%) and seven (10.60%) preterm and term infants, respectively. Multiple lobes involvement was more common in term infants than preterm infants ($P < 0.05$). Subdural hemorrhage, intraparenchymal hemorrhage, and subarachnoid hemorrhage are common in term infants[11]; however, GMH and IVH remain a common and clinically significant problem in preterm infants, particularly extremely preterm infants.[5] Nonetheless, GMH is also noted in term and late preterm infants with PHS.[10,11,16] In the series of Hong and Lee[11] including 42 full-term neonates with intracranial hemorrhage, a total of 16 infants had two or more types of hemorrhage. A single lobe was involved in eight of nine infants with intraparenchymal hemorrhage.[11] In another series, the involvement of a single lobe was seen in nine of 20 full-term infants with supratentorial ICH.[14] Sirgiovanni *et al*.[17] reviewed 36 infants (seven late preterm and 29 term infants) with ICH. They found that all infants with ICH had subdural hemorrhage. Isolated infratentorial subdural hemorrhage was noted in 16 infants (group 1). Both infratentorial and supratentorial subdural hemorrhage were noted in 16 infants (group 2). No additional MRI findings were observed in group 1. However, in group 2, a combination of subdural and subarachnoid hemorrhage was present in two infants, IVH in two infants, and mild white matter abnormalities in six babies. Subdural hemorrhage in both sites (infratentorial + supratentorial) with parenchymal involvement was present in four infants (group 3). The parenchymal involvement consisted of cerebellar hemorrhage in three out of four infants and frontal–parietal hemorrhage in one infant. However, no study has been found about comparison of neuroimaging findings in term and preterm infants with PHS in the literature. In our series, fewer lobe involvements in preterm infants may be related to the immaturity of brain development.

In our series, none of the infants with PHS required the evacuation of hematomas. Hydrocephalus was noted in 32 infants, of whom eight underwent ventriculoperitoneal shunt. Severe mass effect, herniation, or other need for urgent surgical intervention are rare, and management of neonatal hemorrhagic stroke is mostly supportive, including neonatal neurointensive care and seizure monitoring.[1,8] Brouwer *et al*.[14] noted that three infants with a midline shift required craniotomy, six infants needed a subcutaneous reservoir due to outflow obstruction, and three subsequently required a ventriculoperitoneal shunt. In another series, while hydrocephalus was present in 45% subjects, only four required ventriculoperitoneal shunts. No subject had surgical evacuation of hemorrhage.[10] One infant required burr hole drainage of a right parietal epidural hemorrhage, one infant needed a subcutaneous reservoir, and three infants required a ventriculoperitoneal shunt for obstructive hydrocephalus in the series of Hong and Lee.[11]

In our study, eight (12.12%) infants died during infancy period and another patient died at 4 years of age. We found that small for gestational age and mucosal bleeding were more common in infants who are dead than those alive ($P < 0.05$). CP and/or epilepsy and/or hydrocephalus were diagnosed in 36 (85.72%) infants of 42 infants who were followed. Among infants with hydrocephalus, 18 infants had cerebral palsy and/or epilepsy, four infants showed normal neurological development, and other four infants died. Neonates with progressive post-hemorrhagic hydrocephalus are at risk for

adverse neurodevelopmental outcomes. IVH in the setting of prematurity remains the most common cause of acquired hydrocephalus.[18] Brouwer *et al*.[14] reported that the group with poor outcome had a significantly lower 5-min Apgar score (P = 0.006). Three (8.6%) infants developed CP and 13 (24.5%) infants died. The lowest mortality rate was seen in infants with supratentorial ICH (10%).[14] Porcari *et al*.[19] noted that PHS survivors had favorable outcomes in early childhood; at 2 years, moderate to severe deficits occurred in 5%. Language deficits may emerge over time, warranting close follow-up. Three neonates (12%) died during hospitalization; one died later due to cardiac disease. No child developed epilepsy.[19] Bruno *et al*.[10] noted that 47% and 12% infants demonstrated neurologic deficits and mortality, respectively. However, no patient died in the series of Hong and Lee.[11] There is not any data about relationship between small for gestational age, bleeding complaint and mortality in PHS in the literature.

We investigated findings of infants with PHS to compare risk and prognostic factors in preterm and term infants with PHS. However, our study has several limitations. First, this is a retrospective study, and our search might have missed some infants with PHS. Second, not all infants underwent an extensive screening for PHS nor were long-term followed in all infants. Strengths of the study are as follows: The study included a large series of PHS from a single tertiary referral hospital. This is the first cohort study about comparison of risk and prognostic factors in preterm and term infants with PHS in the literature. Our study is also the first study about comparison of lateralization and localization of hemorrhage and brain regions involved in these infants with PHS.

Conclusion

Our findings showed that PHS was much more common in preterm infants than term infants. In PHS, mucosal bleeding and multiple lobes involvement were more common in term infants than preterm infants. PHS had high morbidity and mortality rates. Small for gestational age and mucosal bleeding were more common in infants who are dead than those alive. Further prospective and long-term studies in larger series are needed to explore the risk and prognostic factors in preterm and term infants with PHS.

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Conflicts of interest

There are no conflicts of interest.

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