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Full Length Research Paper

Prevalence, Risk factors and outcomes of Germinal Matrix Intraventricular Hemorrhage in Preterm Babies: A Single Center Study

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Abstract
Germinal matrix intraventricular hemorrhage (GM-IVH) is a major cause of neurological disabilities in preterm babies. This study aimed to determine the prevalence, perinatal risk factors, and outcomes associated with GM-IVH in preterm babies. We conducted a prospective case-control study on preterm infants born at ≤37 weeks of gestation and admitted to the Neonatal Intensive Care Units of the Pediatrics Department, Sohag Faculty of Medicine, Sohag University, Egypt between January 1 2014 and December 31 2014. Of 550 eligible subjects, the prevalence of GM-IVH preterm babies was 74(13.5%). Of these, 15(20.2%) babies had died, 16 (21.6%) cases had post-hemorrhagic hydrocephalus and 11 (14.9%) had periventricular leukomalacia. The risk of GM-IVH was significantly higher in preterm babies with a lower gestational age (P<0.0001) and birth weight (P<0.0001), delivered by normal vaginal delivery (NVD) (P=0.027), in the presence of respiratory distress syndrome (RDS) (P=0.02), needed mechanical ventilation (MV) (P<0.0001), received surfactant therapy (0.002), had sepsis (P=0.002), had hypotension (P<0.0001), or had significant patent ductus arteriosus (PDA) (P=0.001). However, antenatal steroid therapy (P=0.001), delayed umbilical cord clamping (DCC) (P<0.0001), a higher hemoglobin level (P=0.001), and caffeine citrate therapy (P=0.004) seemed to be protective against GM-IVH. The prevalence of GM-IVH preterm babies was 74(13.5%); of them, 15(20.2%) babies died. Prematurity and its sequelae such as RDS, sepsis, MV, surfactant therapy, and PDA are associated with a higher incidence of GM-IVH. Antenatal steroid therapy, DCC, a higher hemoglobin level, and caffeine citrate therapy seem to be protective in reducing the occurrence of GM-IVH.

Keywords: *Intraventricular hemorrhage, preterms, prevalence, risk factors, outcomes.*

Introduction

Prematurity is defined as a birth that occurs before 37 completed weeks. It is associated with approximately one-third of all infant deaths. Infants born preterm are more likely than infants born full term to die during the neonatal period and infancy, and mortality rates increase proportionally with decreasing gestational age or birth weight (1). Germinal matrix intraventricular hemorrhage (GM-IVH) represents the most common form of intracranial hemorrhage, particularly in preterm infants, especially those with a gestational age<32 weeks and birth weight>1500 g (2). The incidence of GM-IVH, inversely proportional to gestational age, has gradually declined in recent decades and currently ranges between 15-25% (3).

The importance of preterm screening by transfontanellar ultrasound (TFUS) is highlighted as babies who are found to have abnormal brain scans are usually asymptomatic. Only occasionally do these patients develop symptoms (seizures or other neurological symptoms) due to a massive intracranial hemorrhage (4). Early identification of brain damage can help in targeting intensive follow-up and adequate rehabilitation (5).The newborn is an uncooperative patient. Thus, cross-sectional modalities such as computed tomography scans or magnetic resonance imaging that require cooperation for optimal image quality are difficult to apply in these fragile infants. Furthermore, the transportation of sick newborns to an imaging facility is often difficult (6).

Transfontanellar ultrasound (TFUS) is the most frequently used method for assessing intracranial abnormalities in the neonatal period. It is less expensive, fast and easily transportable to the bedside. In the neonate and preterm infant, the fontanels and many sutures of the skull are still open, and these can be used as acoustic windows to "look" into the cranium (7). Our institutional neonatal intensive care unit (NICU) provides tertiary level care to newborns in an important low socioeconomic population in Upper Egypt. The unit receives a significant number of preterm babies (<2500 grams) every year.

So far, no data are available regarding the incidence, risk factors, and outcomes of GM-IVH in our hospital. To the best of our knowledge, no study on GM-IVH in premature babies has been published in Upper Egypt. In this study, We examined all preterm babies admitted to our NICU unit over a period of one year by TFUS on days 1, 3 7, and 28 of life (or at discharge) to identify GM-IVH and to assess the relationship between abnormal sonographic data in neonates and neonatal and maternal risk factors. Furthermore, the outcomes of neonates with GM-IVH were evaluated at 28 days of life or at discharge.

Materials and Methods

Patients and methods:

During the study period from January 1 2014 and December 31 2014, we studied the data from 550 preterm babies that were delivered prematurely (less than 37weeks of gestation) and admitted to the Neonatal Intensive Care Unit (NICU) at the pediatrics department, Sohag Faculty of Medicine, Sohag University, Egypt. Data were collected such as sex, gestational age (estimated by the first day of the last menstrual period, first trimester obstetric ultrasound, and standardized scoring systems based on physical and neuromuscular characteristics of the preterm babies, i.e. the New Ballard score (8), birth weight, delivery method, intubation in the delivery room, medications used such as surfactant therapy, caffeine citrate, ibuprofen, and positive inotropic drugs, disease diagnosis and its grade, such as respiratory distress syndrome (RDS), patent ductus arteriosus (PDA), anemia, and thrombocytopenia. Growth measurements, general examination and vital signs were assessed in all preterm babies included in the study. Full term babies, preterm infants with severe congenital malformation, or babies transported to another hospital where excluded from the study. Maternal data such as maternal age, gravidity, in vitro fertilization (IVF), antenatal steroid injections, parent consanguinity, and maternal diseases such as diabetes mellitus, antepartum hemorrhage, preeclampsia/eclampsia, oligohydramnios, and premature rupture of membranes (PROM) were collected.

All subjects were divided into two groups: the GM-IVH group (cases group) and the non-GM-IVH group (control group). The GM-IVH group was subdivided into four grades as proposed by Papile et al. (9). In grade I, the hemorrhage was restricted to the subependymal region/germinal matrix seen in the caudothalamic groove. Grade II hemorrhage extended into normal sized ventricles and typically filled less than 50% of the volume of the ventricle, while grade III hemorrhage extended into dilated ventricles. Grade IV hemorrhage included intraventricular hemorrhage with parenchymal extension. Grade I and II were considered as mild GM-IVH, while Grade III and IV were considered as severe GM-IVH.

All preterm babies were screened by TFUS on days 1, 3, 7 and 28 of life (or at discharge). TFUS was done using a 5MHZ microconvex probe (GE Vivid 3.0 Pro, General Electric, USA). The transducer was applied to the anterior fontanelle with a gel interface that allows penetration of ultrasonic wave in the coronal and sagittal planes. The study was approved by the institutional research committee of the Faculty of Medicine, Sohag University, Egypt. Written informed consent was provided by all parents of the patients included in the study.

Statistical analysis

Clinical, laboratory and radiological data were assessed by using SPSS version 21.0 (SPSS, Chicago, IL, USA). The results of the study were expressed as mean with standard deviation or median with range for continuous variables and as percentages for discrete variables. To compare continuous variables, Student's t-test was used. The chi-squared test was used for categorical variables. Logistic regression analysis was used to assess the independent association between development of GM-IVH and explanatory variables. Variables determined by univariate analysis were entered into the multivariate logistic regression. The odds ratios (ORs) with 95% confidence intervals (CIs) were calculated. A P value <0.05 was considered statistically significant.

Results

In this study, the prevalence of GM-IVH preterm babies was 74(13.5%), while the prevalence of severe GM-IVH (grades III-IV) was 35 (6.4%). As shown in Table 1 and Table (2), the mean (SD) maternal ages were 30.8 (6.08) years with an age range from 19 to 45 years. Mean (SD) gestational age at birth was 31.4 (2.38) weeks with a range of 26-36 weeks. Mean (SD) birth weight was 1217.3 (263.3) grams with a range of 650-2600 grams. In total, there were 292 (53%) male and 258 (47%) females. There were 282 (51.2%) neonates delivery by normal vaginal delivery (NVD) compared to 268 (48.8%) neonates delivered by cesarean section (CS).

As shown in Table 1, there were no statistically significant differences between preterm infants with GM-IVH and the control group with regard to maternal age, parent consanguinity, IVF, PROM, or maternal diseases such as diabetes mellitus, antepartum hemorrhage, preeclampsia/eclampsia, and oligohydramnios. However, preterm infants with GM-IVH were delivered NVD more often than by CS (P=0.027). With regard to the use of antenatal corticosteroids, only 22 (29.7%) preterm babies with GM-IVH received a course antenatal corticosteroids compared to 258 (54.2%) infants in the control group who received at least one course of antenatal corticosteroids (P=0.001).

As shown in Table 2, in our hospital, delayed umbilical cord clamping (DCC) is a standard method for all preterm babies who not need emergency resuscitation; this occurred in 402 (73%) of preterm deliveries included in the study. With our recent decision to avoid intubation of preterm infants in the delivery room and to try non-invasive ventilation instead, in this study, only 92 (16.7%) babies underwent intubation in the delivery room, compared to 458 (83.2%) cases in which intubation was not needed. During the care of preterm infants in the NICU, the prevalence of RDS, mechanical ventilation and surfactant therapy were 289 (52.5%), 122(22.2%), 107(19.5%) respectively. Moreover, there were 81 (14.7%) cases with sepsis proven by blood culture. There were 125 (22.7%) cases of significant PDA requiring therapy with ibuprofen. In this study, the mean (SD) hemoglobin level was 14.46(1.9) g/dl with a range from 8.5 to 18 g/dl, while the mean (SD) platelet count was 171.2(19.4) x 10^9/dl with a range from 30 to 560 x 10^9/dl. As shown also in Table 2, there were no statistically significant differences between preterm infants with GM-IVH and the control group with regard to neonatal gender, multiple births, or platelet counts. However, preterm infants with GM-IVH had a lower gestational age and birth weight than the control group (P<0.0001 for both). Also, this study showed that DCC, a higher hemoglobin level after birth, and the use of caffeine citrate for the treatment of apnea of prematurity had a protective effect against GM-IVH in preterm infants (P<0.0001, 0.001, and 0.004, respectively). Moreover, the need for intubation in the delivery room, the use of mechanical ventilation, and surfactant therapy all increased the incidence of GM-IVH in preterm infants compared to the control group (P<0.0001,<0.0001, and 0.002, respectively). Nevertheless, during the neonatal care of preterm infants in the NICU, preterm infants with RDS, sepsis, significant PDA, hypotension, or the need for positive inotropic drugs had a higher incidence of GM-IVH than the control group (P=0.02, 0.002, 0.001, and <0.0001, respectively).

As shown in Table 3, there were 12 preterm infants with a gestational age ≤28 weeks at birth who had severe GM-IVH (grade III-IV) compared to seven cases with mild GM-IVH (grades I-II). However, with an increase in the gestational age of the preterm infants, the incidence and severity of GM-IVH decreased, so that only four cases with gestational age ≥32 weeks had severe GM-IVH (grade III-IV) and eight cases had mild GM-IVH (grades I-II) compared to 210 preterm infants in the control group.

Table 1. Comparison between case group & control group as regards maternal risk factors of the studied neonates

Maternal characteristics	Case group N= 74	Control group N= 476	Total N= 550	P value
Maternal age				
Mean (SD)	29.86(6.18)	31.34(5.98)	30.8 (6.08)	0.896
Parent consanguinity				
Yes	51 (68.9%)	273(57.3%)	324 (58.9%)	0.066
No	23 (31.1%)	203 (42.7%)	226 (41.1%	
Type of delivery				
Normal vaginal delivery	45 (60.8%)	237 (49.8%)	282 (51.2%)	0.027
C-section.	29 (39.2%)	239 (50.2%)	268 (48.8%)	
Antenatal steroid therapy				
Yes	22(29.7%)	258 (54.2%)	280 (50.9%)	0.001
No	52 (70.3%)	218(45.8%)	270 (49.1%)	
Preeclampsia /Eclampsia				0.277
Yes	13 (17.6%)	106 (22.1%)	119 (21.6%)	
No	61 (82.4%)	370(77.9%)	431 (78.4%)	
Maternal DM				
Yes	8 (10.8%)	47 (9.9%)	55 (10%)	0.5
No	66 (89.2%)	429 (90.1%)	495 (90%)	
IVF				
Yes	15 (20.3%)	94 (19.8%)	109(19.8%)	0.539
No	59(79.7%)	382(80.2%)	441(80.2%)	
Antepartum Hemorrhage	12 (16.2%)	62(13%)	74(13.5%)	0.33
Yes	62 (83.8%)	414 (87%)	476(86.5%)	
No				
Oligohydramnios				
Yes	4 (5.4%)	26(5.3%)	30 (5.5%)	0.609
No	70 (94.6%)	450 (94.7%)	320 (94.5)	
PROM (>18 hr)				
Yes	20 (27%)	120 (25.2%)	140 (25.5%)	0.52
No	54 (73%)	356 (74.8%)	410(74.5%)	

DM: diabetes mellitus; IVF: in vitro-fertilization; PROM: premature rupture of membranes; N: number; SD: standard deviation.

Table 2. Comparison between case group and control group as regards neonatal risk factors of studied preterm babies

Characteristics	Case group N= 74	Control group N= 476	Total N: 550	P value
Gender				
Male	45(60.8%)	247 (51.9)	292 (53%)	0.139
Female	29 (39.2%)	229 (48.1%)	258 (47%)	
Gestational age				
Mean (SD)	29.95 (2.189)	32.23 (2.07)	31.4 (2.38)	<0.0001
Birth weight				
Mean (SD)	1075.5 (214.5)	1297.4 (255)	1217.3 (263.3)	<0.0001
Multiple Birth				
Single	50 (67.6%)	305 (64.1%)	355 (64.5%)	0.367
Twins /triplets	24 (32.4%)	171 (35.9%)	195 (35.5%)	
DCC				<0.0001
Yes	28 (37.8%)	374 (78.6%)	402 (73%)	
No	46 (62.2%)	102 (24.1%)	148 (27%)	
Intubation at delivery				
Yes	34 (45.9%)	58(12.2%)	92 (16.7%)	<0.0001
No	40 (54.1%)	418 (87.8%)	458 (83.2%)	
Mechanical ventilation				
Yes	42(56.8%)	80(14.5%)	122 (22.2%)	<0.0001
No	32(43.2%)	470(85.5%)	428 (77.8%)	
Hypotension				<0.0001
Yes	45 (60.8%)	84 (17.6%)	129(23.5%)	
No	29 (39.2%)	392 (82.4%)	421 (76.5%)	
Sepsis				
Yes	26 (35.1%)	55(11.5%)	81 (14.7%)	0.002
No	48(64.9%)	421 (88.5%)	469(85.3%)	
PDA				
Yes	31 (41.9%)	94 (19.8%)	125 (22.7%)	0.001
No	43 (58.1%)	382 (80.2%)	425 (77.3%)	
RDS				
Yes	49 (66.2%)	240 (50.4%)	289(52.5%)	0.02
No	25 (33.8%)	236 (49.6%)	261(47.5%)	
Caffeine citrate				
Yes	35 (47.3%)	320(67.2%)	355(64.5%)	0.004
No	39(52.7%)	156 (32.8%)	195 (35.5%)	
Surfactant				
Yes	27 (36.5%)	80(16.8%)	107 (19.5%)	0.002
No	47(63.5%)	396 (83.2%)	443 (80.5%)	
Hemoglobin level				
Mean (SD)	12.2 (1.9)	15.03(1.5)	14.46(1.9)	0.001
Platelets count				
Mean (SD)	168.83 (21.062)	172.2(19.526)	171.2(19.4)	0.257

DCC: delayed umbilical cord clamping; RDS: respiratory distress syndrome; PDA: patent ductus arteriosus; N: number; SD: standard deviation.

Regarding the timing of initial detection of GM-IVH at different days of examination in this study, on the first day of examination, 30 (41.7%) preterm babies had GM-IVH, while on the third day 33 (45.8%) new cases had GM-IVH and on the seventh day only 9 (12.5%) new cases developed GM-IVH. Moreover, the severity of (GM-IVH grades) on different days of examination of the studied neonates showed that, on the first day of neonatal life, the prevalence of GM-IVH grades I-IV was 27 (4.9%), 3 (0.5%), 0, and 0, respectively. On the third day of life, the GM-IVH grade I-IV prevalence was 23 (4.2%), 36 (6.5%), 4 (0.7%), and 0, respectively. On the seventh day of life, the prevalence ofGM-IVH grades I-IV was 9 (1.6%), 28 (5%), 25 (4.5%), and 10 (1.8%), respectively. With regard to the outcome of the studied preterm infants with GM-IVH on the 28thday of life or at discharge, there were 28 (37.9%) preterm infants living with normal TFUS, and 15(20.2%) had died. There were 16 (21.6%) cases of post-hemorrhagic hydrocephalus and 11 (14.9%) cases of periventricular leukomalacia. Four (5.4%) cases were lost to follow-up. In Table 4, multivariate logistic regression analysis was performed to assess the factors that reached significance ($p<0.05$) in the univariate analysis. We found that

lower gestational age (odds ratio (OR): 7.99; 95% confidence interval [CI]: 7.994- 8.97, P<0.0001), lower birth weight (OR: 6.60; 95% CI: 6.51-8.71, P<0.0001), NVD (OR: 1.83; 95% CI: 1.03-3.28, P=0.04), the need for intubation in the delivery room (OR: 4.06; 95% CI:2.18-7.57, P<0.0001), the need for mechanical ventilation (OR: 5.94; 95% CI: 3.18-11.09, P<0.0001), the presence of symptomatic hypotension (OR: 7.28; CI: 3.81-13.9, P<0.0001), the presence of proven sepsis (OR: 2.65;95% CI: 1.42-4.94, P 0.002), the presence of significant PDA (OR: 2.91; 95% CI: 1.55-5.47, P 0.001), the presence of RDS (OR: 1.51; 95% CI: 0.845-2.71, P 0.02),and the use of surfactant therapy (OR: 2.84; 95% CI: 1.47-5.5, P=0.002) were associated with an increased risk of GM-IVH.

On the other hand, the use of antenatal corticosteroid injection (odds ratio (OR): 0.358; 95% CI: 0.195-0.655 P=0.001), DCC (OR: 0.165; 95% CI: 0.08-0.31, P<0.0001), the use of caffeine citrate (OR: 0.81; 95% CI: 0.99-3.31, P=0.002), and a higher hemoglobin level (OR: 0.56; 95% CI: 0.47-0.67, P=0.003) were associated with a decreased risk of GM-IVH.

Table 3. The incidence and severity of GM-IVH according to gestational age of the studied preterm babies

		Case N= 74		Control N= 476	Total N: 550
		Grade I-II	Grade III-IV		
Gestational age at birth	≤ 28 Weeks	7 (17.9%)	12 (34.3%)	12 (2.3%)	31(5.7%)
	29-32 Weeks	24 (61.5%)	19 (54.3%)	254 (53.4%)	297 (54%)
	≥ 32 Weeks	8 (20.5%)	4 (11.4%)	210 (44.3%)	222 (40.3%)
Total		**39 100%**	**35 100%**	**476 100%**	**550 100%**

Table 4. Multivariate logistic regression analysis of neonatal and maternal risk factors of the case and control groups

Characteristics	Odds ratio	95% CI	P value
Gestational age	7.99	7.994-8.97	<0.0001
Birth weight	6.60	6.51-8.71	<0.0001
Type of labor	1.83	1.03-3.28	0.04
Antenatal steroid therapy	0.358	0.195-0.655	0.001
DCC	0.165	0.08-0.31	<0.0001
Intubation at delivery	4.06	2.18-7.57	<0.0001
Mechanical ventilation	5.94	3.18-11.09	<0.0001
Hypotension	7.28	3.81-13.9	<0.0001
Sepsis	2.65	1.42-4.94	0.002
PDA	2.91	1.55-5.47	0.001
RDS	1.51	0.845-2.71	0.02
Caffeine citrate	0.81	0.99-3.31	0.002
Surfactant	2.84	1.47-5.5	0.002
Hemoglobin level	0.56	0.47-0.67	0.003

95% CI: confidence for interval; DCC: delayed umbilical cord clamping; PDA: patent ductus arteriosus; RDS: respiratory distress syndrome.

Discussion

Ultrasonography and Doppler studies play a very important role in the early diagnosis and management of high-risk neonates. TFUS is currently the primary imaging modality employed in the assessment of the neonatal brain. This prospective study included 550 preterm infants; 53% were males and 47% were females. All cases were examined by TFUS on day 1, 3, 7, and 28 of life (or at discharge). The prevalence of any degree of GM-IVH in this study was 74(13.5%) cases; severe GM-IVH (grades III-IV) was observed in 35 (6.4%) preterm babies. Previous studies showed an incidence of GM-IVH around 15-40% which is comparable with our results (10). This prevalence is lower than that found by Brezan et al. in 2012 (11), in which the prevalence of all types of IVH assessed over a five-year period was 20.4% in a cohort of 1480 preterm infants. The prevalence observed in the present study is also lower than that reported by Horbar et al. (3), who estimated overall GM-IVH rates of 20% to 25% in the period from 1991 to 1999. Our prevalence is greater than that found by Rong et al. (12) in China where the incidence of GM-IVH in babies<34 weeks was

3.9%.This may be explained by; in the present study all grades of GM-IVH and all preterm infants with less than 37 weeks gestational age were included.

GM-IVH originates in the subependymal germinal matrix layer of the developing brain with possible rupture into the ventricular system. The subependymal region is full with a tight net of weak capillaries. This layer gradually decreases in size as the fetus matures (13). TFUS in the first week of life reveals the vast majority of GM-IVH cases, since 90% of these occur within the first 72 hours of life (9). Serial TFUS was important for the detection GM-IVH, as in the present study, on the first day of examination, 30 (41.7%) preterm babies had mild GM-IVH (grade I-II) and no cases of severe GM-IVH (grade III-IV) were detected. Severe GM-IVH started to appear on the third day (four cases) and on the seventh day (35 cases) of examination.

Regarding the outcome among the studied neonates with GM-IVH on the day 28thof life, the mortality rate in our study was 15 (20.2%) of cases. This mortality rate is comparable with the findings of Linder et al. (14). Regarding the development of post-hemorrhagic hydrocephalus as a complication of GM-IVH, it was present in 16 (21.6%) cases in our study, similar to the findings of Sajjadian et al. (15) who showed that post-hemorrhagic hydrocephalus developed in 20% of preterm babies with GM-IVH. Dykes et al. (16) reported that the incidence of post-hemorrhagic hydrocephalus in 409 preterm babies weighing less than 1500 grams was 13%. Periventricular leukomalacia (PVL) was observed in 14.9% of cases in our study. In a study by Szymonowicz et al. (17), five survivors of GM-IVH developed PVL between three and seven weeks of age.

GM-IVH is common in preterm babies and it leads to significant sequelae such as cerebral palsy and mental retardation (15). Therefore, it is very important to identify the risk factors associated with the development of GM-IVH. Several maternal and neonatal risk factors for the development of GM-IVH have been reported. According to our study, we did not find any relation between the incidence of GM-IVH and maternal age; this agrees well with other studies (14, 18, 19). Moreover, parent consanguinity in our study was not associated with an increased risk of GM-IVH or adverse outcomes; this does not agree with the findings of Qandalji et al. (20), who found that consanguinity has an adverse effect on pregnancy and neonatal outcomes.

NVD was significant risk factor for GM-IVH in our study and CS seemed protect against the development of GM-IVH. Many other studies (21, 22, 23) have confirmed the higher incidence of GM-IVH with NVD of preterm babies, and selective CS seems to be protective, in some cases, against severe GM-IVH. However, other studies (18, 24, 25) have not revealed any relationship between the mode of delivery and GM-IVH. Furthermore, Dani et al. (26) and Wylie et al. (27) reported that CS does not improve neonatal survival of very low birth weight infants but only decreases the occurrence of GM-IVH.

Antenatal use of corticosteroids has been reported to be a protective factor against the occurrence of GM-IVH; in the present study, with the use of multivariate logistic regression analysis, corticosteroid use was associated with a decreased risk of GM-IVH. The protective mechanism may be due to an increase in neonatal blood pressure, which prevents blood pressure fluctuations or may result from enhanced maturation of the cardiopulmonary system and germinal matrix of the premature infant (21).The protective effect of antenatal steroids in our study agrees well with several other studies (19, 25, 21, 28, 29).

This study did not find any influence on the incidence of GM-IVH with preeclampsia/ eclampsia, maternal diabetes mellitus, antepartum hemorrhage, oligohydramnios, PROM, multiple births, in vitro fertilization, or platelet counts. Moreover, our results confirm the results of other studies (14, 24, 29, 30) in that male gender did not increase the risk of GM-IVH. However, these results disagree with other studies (31, 32, 33) that found that male gender increases the risk of GM-IVH.

Low gestational age & low birth weight are well-known risk factors for GM-IVH, as already reported by others in larger series (14, 34, 35, 36). In this study, gestational age and birth weight were independent risk factors of GM-IVH in the multivariate logistic analysis. Consequently, the prevention of prematurity would be the most effective means of reducing the incidence of GM-IVH. A program for the prevention of prematurity must emphasize the early identification of women at risk of preterm delivery, early diagnosis, and in utero transfer to a tertiary perinatal center (37). Nevertheless, Kim et al. (19) reported that gestational age and not birth weight is an independent risk factor for GM-IVH.

We found no significant difference in the occurrence of GM-IVH between infants born after in vitro fertilization and those born without assisted conception. This agrees with the findings of Lee et al. (29) and Haroon et al. (30). However, Linder et al. (14) reported that infants born after IVF have a higher incidence of neurologic impairment and GM-IVH. Moreover, DCC was found in our study to be strongly associated with a decreased incidence of GM-IVH, as noted in our multivariate logistic regression analysis. Our results agree with previous studies showing that DCC provides important clinical benefits and decreases the incidence of GM-IVH in preterm infants (38, 39, 40). In this study, the risk of GM-IVH was significant in premature infants who underwent intubation in the delivery room. Our results agree with those of Pekcevik et al. (28) and Aly et al. (41) but disagree with those of Linder et al. (14), who reported no significant risk associated with intubation in the delivery room and the occurrence of GM-IVH in premature infants. Moreover, premature babies requiring mechanical ventilation either in the resuscitation room or in the NICU were found to have a

greater risk of GM-IVH. This may be due to the severity of the illness or may be associated with fluctuations in blood pressure in the premature infant, which is thought to be the main cause of GM-IVH (21, 42). Decreases in cerebral blood flow, occurring either prenatally or postnatally, may cause injury to germinal matrix vessels in about 20-45% of premature infants (43). In this study, systemic hypotension not only increased the incidence of GM-IVH, but was also associated with the occurrence of high-grade GM-IVH, a finding that has also been reported in other studies (14, 25, 44, 45). However, some older reports found no association between hypotension and GM-IVH (46, 47).

In this study, sepsis was as significant risk factor for GM-IVH in the logistic regression analysis.This agrees well with other studies (21, 25, 42, 48). Sepsis increases the incidence of GM-IVH due to damage to the fetal blood-brain barrier mediated by cytokines (21). Furthermore, Linder et al. (14) found that early sepsis was associated with an eight-fold increase in the incidence of GM-IVH. The results of Haroonet al. (30) and Pekcevik et al. (28) disagree with our findings, as they did not find a significant relationship between sepsis and the occurrence of GM-IVH in premature infants. This may have been due to early onset antibiotic therapy (28, 30).

The presence of PDA in preterm babies is a significant risk factor for the development of GM-IVH, in agreement with studies by Kim et al. (19) and Lee al. (29). However, our study disagrees with the findings of Haroon et al. (30), who found no significant relationship between the presence of PDA and the occurrence of GM-IVH in premature infants. Furthermore, the present study demonstrated a significance relationship between RDS and the occurrence of GM-IVH.This may occur because babies with severe RDS need to put on mechanical ventilation. This agrees well with other studies (18, 30, 49, 50), but our results disagree with the findings of Kim et al. (19), Lee et al. (29), and Linder et al. (14), where no significant relationship between RDS and the occurrence of GM-IVH was found.

We found that the risk of developing GM-IVH was three-fold higher in preterm babies receiving surfactant therapy in our multivariate logistic analysis. Our results are comparable to those of Haroon et al. (30), in which babies with a diagnosis of GM-IVH had a four-fold greater chance of receiving surfactant than non-GM-IVH infants. However, our results contradict those of Linder et al. (14), who found no significant relationship between the occurrence of GM-IVH and surfactant therapy in premature infants.

In this study, we found that a lower hemoglobin level at birth was significantly associated with a higher incidence of GM-IVH in the univariate and multivariate analysis. Similar to our findings, Hosono et al. (51) reported an increased incidence of GM-IVH in extremely low birth weight infants with a hemoglobin level at birth<15 g/dl. Furthermore, Linder et al. (14) demonstrated that a low initial hematocrit is associated with a higher incidence of GM-IVH. An increased hemoglobin level at birth as a result of DCC has been demonstrated to reduce the risk of GM-IVH in premature infants.

Conclusion

The prevalence of GM-IVH was decline in the recent years due to increased awareness of prevention of prematurity. In this study, it was 13.5%, whereas the mortality still high as there were 20.2% of cases were died. The risk factors of GM-IVH in preterm babies had diversity between literatures. In this study, NVD increased the risk of GM-IVH. Moreover, Prematurity and its sequelae such as RDS, sepsis, MV, surfactant therapy, and PDA are associated with a higher incidence of GM-IVH. Antenatal steroid therapy, DCC, a higher hemoglobin level, and caffeine citrate therapy seem to be protective in reducing the occurrence of GM-IVH.

Conflict of interest statement

The authors had no conflict of interests.

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