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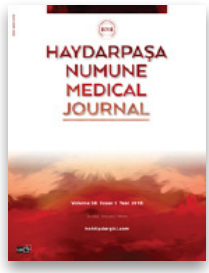

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ORIGINAL ARTICLE

Evaluation of Intracranial Hemorrhage Incidence and Risk Factors in Very Low Birth Weight Preterm Newborns

Selim Sancak, Sevilay Topcuoğlu, Güner Karatekin

Deparment of Neonatology, Ministry of Health, University of Health Sciences Turkey, Zeynep Kamil Maternity and Children's Hospital, İstanbul, Turkey

Abstract

Introduction: To investigate Intracranial Hemorrhage Incidence (ICH) and Risk Factors in Very Low Birth Weight Preterm Newborns.

Methods: Data of 816 preterm newborns with birth weight (BW) <1500 g [24-32 weeks of gestation (GW)] followed in our unit over a four-year period (2011-2014) were retrospectively analyzed in terms of ICH and risk factors. The data of the newborns with and without ICH were compared with Student T and Chi-square tests. Independent risk factors that are effective on ICH were determined by logistic regression analysis.

Results: Average gestational week and birth weight of 232 patients with ICH were 27.6±2.2 weeks and 945±241 g, respectively and the incidence of ICH was found 28.4% (grade I, II, III and IV ICH rates; 12.4%, 6.6%, 6% and 3.4%, respectively). In single variable comparison, GW (p<0.001), BW (p<0.001), vaginal birth (p=0.014), resuscitation (p<0.001), respiratory distress syndrome (RDS) (p<0.001), mechanical ventilation (MV) (p<0.001), high frequency oscillatory ventilation (HFOV) (p<0.001), nasal intermittent positive pressure (NIPPV) (p<0.001), patent ductus arteriosus (PDA) (p<0.001), sepsis (p<0.001), erythrocyte transfusion (p<0.001), pneumothorax (p= 0.017) and inotrope use (p<0.001) were found statistically significant. In logistic regression analysis, resuscitation [relative risk (RR): 1.85, confidence interval (Cİ): 1.13-3.04], PDA (RR: 1.74, Cİ: 1.19-2.53), erythrocyte transfusion (RR: 1.87, Cİ: 1.24-2.82), MV (RR: 2.19, Cİ: 1.24-3.88), HFOV (RR: 1.61, Cİ: 1-2.59) and NIPPV (RR: 1.61, Cİ: 1.13-2.32) were detected as significant independent risk factors.

Discussion and Conclusion: Despite the advancing technology, the desired reduction in the ICH frequency could not be achieved due to the increase in the survival numbers of immature newborns. Efforts should be made to reduce the risk factors mentioned.

Keywords: Intracranial hemorrhage; preterm newborn; very low birth weight.

Intracranial hemorrhage (ICH) is an important cause of brain damage in premature newborns. Although its incidence has been decreasing since 1980s, ICH continues to be a significant problem due to the increase in survival rates of extremely premature newborns[1].

Intracranial hemorrhage is generally seen in preterm newborns with <32 gestation weeks (GW) or <1500 g birth weight (BW), and its frequency increases as the gestational age and birth weight decrease. In the late 1990s, the incidence of ICH in very low birth weight newborns in the United States was reported as 20% whereas it was 45% for infants with extremely low birth weight[2].

ICH in preterm newborns is caused by hemorrhage from fragile blood vessels in the germinal matrix. It is shown in neuropathological studies that hemorrhage primarily originates from the capillary network connected directly with

Correspondence (İletişim): Selim Sancak, M.D. Saglik Bilimleri Universitesi Zeynep Kamil Kadin Dogum ve Cocuk Hastaliklari SUAM, Neonatoloji Klinigi, Istanbul, Turkey
Phone (Telefon): +90 535 428 22 24 **E-mail (E-posta):** drselimsancak@gmail.com
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venous vessels. These veins are existed in the area among the cerebral arteries and deep collector veins. Hemorrhage may disrupt the ependymal line and spread into the lateral ventricle. The severity of hemorrhage varies depending on its remaining limited in the germinal matrix or its spreading to adjacent system or intraparenchymal area[3].

ICH in premature newborns is considered to be due to germinal matrix and fluctuations in cerebral blood flow stemming from the lack of structural support due to immaturity[4]. The germinal matrix that produces neuron and glia cells during the fetal development consists of a large amount of cellular and capillary vessels. As the fetus matures, the germinal matrix cellularity and vascularity decrease and undergo involution starting from the 28 GW and disappears completely at the term age[5]. The capillary network in the germinal matrix consists of large numbers of thin-walled blood vessels without structural support. These vessels have a fragile structure due to immature basal lamina, lack of pericytes and tight junctions, and lack of glial fibrillar acidic protein in the astrocyte feet[4]. Due to these structural deficiencies, germinal matrix vessels inclined to hemorrhage as a result of fluctuations in cerebral blood flow. The fragile capillary network drains into the terminal vein connected to the internal cerebral vein. It has been suggested that venous system congestion due to increased cerebral venous pressure may cause hemorrhage in the germinal matrix[6].

Transfontanel ultrasound is the most commonly used screening method for the diagnosis of ICH due to its high sensitivity, portability, and being radiation free. Coronal and parasagittal plans are used routinely. Ultrasonography enables ICH staging with high accuracy. Since no symptoms are appeared on approximately half of intracranial hemorrhage cases, routine ultrasound screening should be performed[3]. In our unit, ICH screening is performed with routine transfontanel ultrasonography on the 1st, 2nd, 3rd, 7th, 14th and 28th days for each newborn <32 GW.

Since it causes mortality and long-term neurodevelopmental problems, it is important to take the necessary measures to determine and prevent the frequency and risk factors of ICH. In this study, we aimed to determine the frequency of ICH and the risk factors that are effective in very low birth weight preterm newborns born in our unit.

Materials and Methods

The patient files who were born between January 2011 and December 2014 at the S.B SBÜ Zeynep Kamil Obstetrics and Pediatrics Training and Research Hospital and followed up in the Neonatology Clinic, and who were screened via transfontanel ultrasonography for ICH because of their 24-32 GW and <1500 g BW, were researched retrospectively. The antenatal and clinical characteristics of the patients and the results of ICH screening were recorded. The patients were classified according to their GW and BW, and the frequency of ICH was determined.

Gestation week was calculated through the last menstrual period and the new Ballard score[7]. Newborns with birth weight <10th percentile were classified as low (SGA) by GW, those between 10 and 90 percentile as proper (AGA) by GW and those with >90th percentile were classified as great (LGA) by GW.

Papile classification was used for staging intracranial hemorrhage: Stage I: Limited hemorrhage to the germinal matrix, Stage II: Intraventricular hemorrhage and normal ventricle width, Stage III: Intraventricular hemorrhage and ventricular dilatation, and Stage IV: Intraventricular hemorrhage and spread of bleeding into the adjacent brain parenchyma. Stage I and II hemorrhages were classified as mild and stage III and IV hemorrhages as severe[8].

Cases in which antibiotic treatment was initiated following clinical observation and laboratory tests as well as which had positive blood culture were accepted as sepsis. The criteria for the diagnosis of hemodynamically significant patent ductus arteriosus (PDA) were accepted as left atrium/aortic root >1.4 and ductus diameter/DA >1.4. The cases that received two doses of antenatal steroid were considered to have a complete cure, while those had an incomplete cure were considered not receiving antenatal steroids. Bell's classification was used in the diagnosis of necrotizing enterocolitis (NEC)[9]. Bancalari Criteria were used for the diagnosis of bronchopulmonary dysplasia (BPD)[10].

SPSS (Statistical Package for the Social Sciences) 17.0 program was used for statistical analysis. Groups with and without intracranial hemorrhage were compared in terms of risk factors by single ratio comparisons (independent groups Student T and Chi-square tests). Findings were given as average±standard deviation. Risk factors with significant differences were examined in terms of independent risk factors by logistic regression analysis and independent risk factors were determined. A P value that is less than 0.05 was considered statistically significant.

Results

Matching with our criteria a total of 816 cases were evaluated during the study period. While the average GW of

232 (28.4%) patients with intracranial hemorrhage was 27.6±2.2 weeks and BW 945±241 g, 584 patients without ICH were 28.9±2 weeks and 1106±263 g. The frequency of intracranial hemorrhage was 29.9% in girls and 27% in boys. It was found that the rate of intracranial hemorrhage increased as the GW and BW decreased. The frequency of ICH by gestational week and BW is shown in Table 1.

When the cases with intracranial hemorrhage are evaluated according to the stages; Stage I, II, III and IV ICH rates were found 12.4% - 6.6 - 6 and 3.4%, respectively (Table 2). Stage IV ICH rate was 6.5% at 24-26 GW, while it decreased to 1% at 30-32 GW. It was observed that the frequency of intracranial hemorrhage increased below 28 GW and 1000 g BW.

The frequency of mild ICH was 18.9% in the entire patient population, while the frequency of severe ICH was 9.4%. The frequency of severe ICH was 18.4% in the 24-28 GW range, while it was 3.1% in the 28-32 GW range (Table 3).

In the single rates comparison between patients with and without intracranial hemorrhage, GW, BW, vaginal delivery, resuscitation, chorioamnionitis, RDS, MV, HFOV, inotrop use, erythrocyte transfusion, sepsis, PDA, premature retinopathy (ROP) and stage II-III NEC showed statistically significant difference (Table 4).

When logistic regression analysis is applied to variables having statistically significant difference in univariate analyzes; resuscitation [Relative risk (RR): 1.85], NIPPV (RR: 1.61), PDA (RR: 1.74), MV (RR: 2.19), HFOV (RR: 1.61) and erythrocyte transfusion (RR: 1.87) were determined as an independent risk for ICH factors (Table 5).

Table 1. Classification of cases with and without intracranial hemorrhage by gestational week and birth weight

	ICH (+)	ICH (-)	Total
Girl/Boy (%)	120 (29.9)/112 (27)	281 (70.1)/303 (73)	401 (49)/415 (51)
Gestational week	27.6±2.2	28.9±2	28.5±2.1
24-26 week (n,%)	68 (49.3)	70 (50.7)	138
26-28 week (n,%)	76 (38.2)	123 (61.8)	199
28-30 week (n,%)	51 (19)	218 (81)	269
30-32 week (n,%)	37 (17.6)	173 (82.4)	210
Birth weight (g)	945±241	1106±263	1060±267
500-750 g (n,%)	57 (43.8)	73 (56.2)	130
750-1000 g (n,%)	84 (39.8)	127 (60.2)	211
1000-1250 g (n,%)	57 (25.7)	165 (74.3)	222
1250-1500 g (n,%)	34 (13.4)	219 (86.6)	253
Total (n,%)	232 (28.4)	584 (71.6)	816

ICH: Intracranial Hemorrhage.

Table 2. Evaluation of cases with intracranial hemorrhage by stages.

	Stage I ICH	Stage II ICH	Stage III ICH	Stage IV ICH
Gestational week				
24–26 week (n,%)	16 (11.6)	22 (15.9)	21 (15.2)	9 (6.5)
26-28 week (n,%)	30 (15.1)	14 (7)	19 (9.5)	13 (6.5)
28-30 week (n,%)	32 (11.9)	10 (3.7)	5 (1.9)	4 (1.5)
30-32 week (n,%)	23 (11)	8 (3.8)	4 (1.9)	2 (1)
Birth weight (g)				
500-750 g (n,%)	15 (11.5)	17 (13.1)	14 (10.8)	11 (8.5)
750-1000 g (n,%)	34 (16.1)	19 (9)	23 (10.9)	8 (3.8)
1000-1250 g (n,%)	30 (13.5)	11 (5)	9 (4.1)	7 (3.2)
1250-1500 g (n,%)	22 (8.7)	7 (2.8)	3 (1.2)	2 (0.8)
Total (n,%)	101 (12.4)	54 (6.6)	49 (6)	28 (3.4)

ICH: Intracranial Hemorrhage.

Table 3. Frequency change of mild and severe intracranial hemorrhage by gestation week and birth weight.

	Stage I-II ICH	Stage III-IV ICH	Total Cases
Gestational week			
24-28 week	82 (24.3)	62 (18.4)	337
28-32 week	73 (15.2)	15 (3.1)	479
Birth Weigh (g)			
500-1000 g (n,%)	85 (14.3)	56 (16.4)	341
1000-1500 g (n,%)	70 (14.7)	21 (4.4)	475
Total (n,%)	155 (18.9)	77 (9.4)	816

ICH: Intracranial hemorrhage.

Table 4. Comparison of cases with intracranial hemorrhage in terms of risk factors.

	ICH (+) (n= 232)	ICH(-) (n= 584)	p
GW (week)	27.6±2.2	28.9±2	<0.001
BW (g)	945±241	1106±263	<0.001
Girl/Boy, n (%)/n (%)	120 (51.7)/112 (48.3)	281 (48.1)/303 (51.9)	0.352
SGA, n (%)	43 (18.5)	76 (13)	0.044
Vaginal Birth, n (%)	47 (20.3)	78 (13.4)	0.014
Multiple pregnancy, n (%)	47 (20.3)	108 (18.5)	0.562
Antenatal steroid, n (%)	105 (45.3)	291 (49.8)	0.239
Resuscitation, n (%)	205 (88.4)	368 (63)	<0.001
Oligohydroamnios, n (%)	23 (9.9)	65 (11.1)	0.613
Early membrane rupture, n (%)	56 (24.1)	146 (25)	0.797
Corioamnionitis, n (%)	21 (9.1)	32 (5.5)	0.062
Preeclampsia, n (%)	48 (20.7)	154 (26.4)	0.09
RDS, n (%)	210 (90.5)	355 (60.8)	<0.001
MV, n (%)	213 (91.8)	358 (61.3)	<0.001
MV duration, day	10.1±12.8	3.1±6.8	<0.001
HFOV, n (%)	56 (24.1)	47 (8)	<0.001
HFOV duration, day	1.5±4.7	0.27±1.3	<0.001
CPAP, n (%)	156 (67.2)	367 (62.8)	0.237
CPAP duration, day	4.6±6	3.1±4.7	0.001
NİPPV, n (%)	136 (58.6)	187 (32)	<0.001
NİPPV duration, day	5.3±8.6	1.6±4	<0.001
BPD, n (%)	107 (46.1)	94 (16.1)	<0.001
Severe BPD, n (%)	14 (6)	6 (1)	<0.001
PDA, n (%)	117 (50.4)	122 (20.9)	<0.001
Inotropy Use, n (%)	131 (56.5)	178 (30.5)	<0.001
Erythrocyte transfusion n (%)	169 (72.8)	205 (35.1)	<0.001
Platelet transfusion n (%)	82 (35.3)	80 (13.7)	<0.001
Pneumothroax, (%)	18 (7.8)	22 (3.8)	0.017
Sepsis, (%)	170 (73.3)	251 (43)	<0.001
NEK stage 2-3, (%)	18 (7.8)	18 (3.1)	0.003
ROP, (%)	121 (52.2)	227 (38.9)	0.001
ROP interference, (%)	52 (22.4)	55 (9.4)	<0.001
Hospitalization Duration	50.6±35.6	36.6±28	<0.001
Mortality, (%)	81 (34.9)	118 (20.2)	<0.001

ICH: Intracranial bleeding; GW: gestation week; BW: Birth weight; SGA: Low birth weight by gestation week; RDS: Respiratory distress syndrome; MV: Mechanical ventilation; HFOV: High frequency oscillatory ventilation; CPAP: Continuous positive airway pressure; NIPPV: Nasal intermittent positive pressure ventilation; BPD: Bronchopulmonary dysplasia; PDA: Patent ductus arteriosus; NEC: Necrotizing enterocolitis; ROP: Retinopathy of prematurity.

Table 5. Effective independent risk factors in intracranial hemorrhage etiology

	OR	%95 CI	p
Resuscitation	1.85	1.13-3.04	0.015
NİPPV	1.61	1.13-2.32	0.009
PDA	1.74	1.19-2.53	0.004
MV	2.19	1.24-3.88	0.007
HFOV	1.61	1-2.59	0.052
Erythrocyte transfusion	1.87	1.24–2.82	0.003

OR: Odds ratio; CI: Confidence interval; NIPPV: Nasal intermittent positive pressure ventilation; PDA: Patent ductus arteriosus; MV: Mechanical ventilation; HFOV: High frequency oscillatory ventilation; p<0.05 statistically significant.

Discussion

In our study, we found that ICH rates decreased with the increase in GW and BW in premature newborns, and factors such as resuscitation, MV, HFOV, and erythrocyte transfusion were independent risk factors for ICH. However, prematurity is the most important risk factor affecting the formation of HRC. In a population-based study, it was revealed that there was a 3.5% decrease in the frequency of ICH in 2896 preterm newborns below 32 GW with an increase in GW per week[11]. In a prospective study involving preterm newborns born below 27 GW between 2004 and 2007 in Sweden, it was observed that the prevalence of ICH was 5.2% in those born at 26 weeks, while this rate increased to 20% in those born at 23 GW[12].

In another study, the frequency of ICC in 9575 preterm newborns (22-28 GW and 401-1500 g BW) was found to be 36% and it was shown that the frequency increased with the decrease in GW. In the same study, it was found that the frequency of severe ICH (stage III and IV) decreased from 26% in 24 GW to 7% in 28 GW[13]. In our study, it was shown that the frequency of ICC between 24 and 28 GW was 42.7%, while the frequency of severe ICH decreased from 18.4% between 24 to 28 GW to 3.1% between 28-32 GW.

In their study Tarcan et al.[14] in which they evaluated 93 preterms with very low birth weight between 1999 and 2002, they found the ICH frequency 24% and neonatal transport, RDS and pneumothorax were found to be significantly higher in the group with ICH. The frequency of ICH at all stages in our study was found 28.4%.

In a retrospective study conducted by Dursun et al. with 246 preterm newborns born with a GW less than 1500 g between 2007 and 2011, the frequency of ICH was found 25.2%. While a significant relationship was found between RDS and PDA with ICH, not a significant relationship between SGA and antenatal steroid use with ICH was found[15]. In our study, a significant correlation was found between RDS and PDA with ICH, but no similar difference was found in terms of antenatal steroid use. Although it has been shown in older studies[16] that SGA newborns have less ICH than those born with AGA, it has been mentioned in recent studies that there is no difference between them[17]. Differently, in our study, the SGA ratio was found statistically significant higher in the group with ICH compared to the group without ICH.

ICH risk factors generally occur due to pathological conditions such as fluctuation in cerebral blood flow due to rapid fluid infusion or increased cerebral venous pressure due to compression of the fetal head during delivery. It has been shown that fluctuations in cerebral blood flow are associated with ICH[3,18]. This situation is particularly apparent in preterm newborns because cerebral blood flow autoregulation mechanisms in preterm newborns are insufficient compared to term newborns. This insufficiency causes cerebral flow that changes passively with blood pressure. Preterm newborns cannot maintain a constant cerebral blood flow during changes in blood pressure[19]. As a result, this causes fragile germinal matrix hemorrhages.

In cases where increased ICH is at risk in babies of mothers with chorioamnionitis[20]. In our study, although the rate of chorioamnionitis was found higher in the group with ICH compared to the group without ICH, statistical significance could not obtained. In case of prolonged premature rupture membranes the ICH incidence was shown to decrease with the use of antibiothreapy[21].

The studies on the relationship between preeclampsia and HRC are contradictory. While it was shown in a large cohort study[22] that preeclampsia increased the risk of ICH 3.2 times, another multicentered study suggested that there was a significant decrease in the frequency of stage II-IV ICH in babies of preeclamptic mothers[23]. Although we found the preeclampsia rate higher in the group without ICH (26.4%) compared to the group with ICC (20.7%) in our study, no statistically significant difference was found.

It was shown that the use of antenatal steroids decreases the risk of ICH[12,24]. On the contrary, in our study, the rates of antenatal steroids were found similar in both groups. The effect of delivery method on ICH frequency is still uncertain. In a prospective cohort study, early transfontanel ultrasound was performed in 254 preterm newborns with a GW of <30, and preterms with early ICH were shown to be babies born vaginally[25]. In another single centered study

evaluating preterm newborns with <28 GWs, the incidence of ICH was found 45% in vaginal delivery and 20% in cesarean delivery[26]. In our study, the rate of vaginal delivery was found significantly higher in the group with ICH. In another retrospective single-centered study, the effect of delivery type on ICH in 934 preterm newborns <1500 g was not shown[27].

It has been shown that the frequency of ICH decreases with late clamping of the umbilical cord[28]. RDS results fluctuations in cerebral blood flow by causing hypocapnia, hypercapnia and acidemia[29]. In our study, the rate of RDS was found statistically significant higher in the group with ICH compared to the group without ICH.

Increasing arterial blood pressure during aspiration of secretions or rapid fluid bolus infusions increases cerebral blood flow[3]. Bicarbonate infusion increases the risk of ICH by causing hyperosmolarity[3]. Mechanical ventilation increases the frequency of ICH by causing fluctuations in cerebral blood flow[30]. In our study, mechanical ventilation and HFOV were found statistically significant higher in the ICH group. Application of resuscitation in the delivery room has been shown to increase the risk of ICH and serious ICH in newborns with a GW of <28[31]. In our study, the rate of resuscitation in the delivery room was found statistically highly significant in favor of ICH.

Numerous studies support the relationship between pneumothorax and ICH due to increased cerebral venous pressure[3,32]. In our study, the rate of pneumothorax was found statistically significant higher in the ICH group compared to the group without it. In another study, there was no increase in ICH frequency in 62 cases with pneumothorax among 675 preterm newborns with <28 GWs compared to cases without pneumothorax[33].

Conclusion

In our study, it is seen that the frequency of ICH is still high. Based on the data we obtained, we found that many prematurity and low GW-related conditions such as RDS, PDA, mechanical ventilation and inotrope use were associated with ICH In addition to improving the quality of care for the preterm baby, since the most important risk factor affecting the formation of ICH is prematurity, the decrease in the frequency of ICH with the increase of GW in preterm newborns and the prevention of premature births will be the most effective factors in the reduction of ICH cases. In conclusion, prevention of prematurity and improvement of neonatal care should be the most important goals in ICH prevention.

Ethics Committee Approval: The Ethics Committee of Zeynep Kamil Training and Research Hospital provided the ethics committee approval for this study (161 / 8.12. 2017).

Peer-review: Externally peer-reviewed.

Authorship Contributions: Concept: S.T., G.K.; Design: S.T., G.K.; Data Collection or Processing: S.S.; Analysis or Interpretation: S.S.; Literature Search: S.S.; Writing: S.S., S.T.

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