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INTRAVENTRICULAR HEMORRHAGE IN PRETERM NEWBORNS*

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Intraventricular hemorrhage (IVH) originating from germinal matrix is the major brain injury of the premature. We studied IVH incidence and risk factors which are implied in this pathology in newborns, hospitalized in the neonatal intensive care unit (NICU) of İstanbul University Cerrahpaşa Faculty of Medicine. Ninety-seven premature newborns with a birth weight of less than 2500 g were examined systematically with cranial ultrasonography (CU). Mean birthweight was 1540 ± 430 g (720-2450) and gestational age 31.6 ± 2.4 weeks (26-37). IVH was diagnosed in 40 cases (41%). The significant risk factors are prematurity (gestational age < 33 weeks), artifical ventilation and infusion of fresh frozen plasma. *Key words: intraventricular, hemorrhage, newborn, risk factors.*

Intraventricular hemorrhage (IVH) originating from germinal matrix is the major brain injury of the premature. Even though screening procedures are becoming more efficient, contrary to expectation, its incidence is decreased. This is obviously directly related to the advancements in perinatology and neonatology. While IVH incidence ranged from 34 to 49 percent in prematures in the early 1980's[1,2], it decreased to about 20 percent in the late 1980's[3]. Perlman and Volpe[4] classified IVH according to birth weight and found that it was seen with an incidence of 25 percent between 700-1500 g and 62 percent in weights of less than 700 g. In another study, 50 percent of IVH was found in the first, 25 percent in the second and 15 percent in the third 24 hours. Many factors, such as birth weight, gestational age, Apgar score, base deficit in umbilical cord blood, low mean arterial pressure, infusion of volume expanders, tracheal intubation, surfactant application and presence of symptomatic patent ductus arteriosus (PDA), are implied in the pathogenesis of IVH[5].

In the study of Hope et al.[6], results of cranial ultrasonography assessment were compared with autopsy findings in the brains of 56 infants with a gestational age of less than 33 weeks, to determine the diagnostic accuracy of ultrasonography in detecting IVH. Ultrasound identified IVH with a sensitivity of 91 percent and a specificity of 81 percent intraparenchymal hemorrhage with

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a sensitivity of 82 percent and a specificity of 97 percent, and germinal matrix hemorrhage with a sensitivity of 61 percent and a specificity of 78 percent.

The aim of this retrospective study is to show IVH incidence in our neonatal intensive care unit (NICU) and risk factors which are implied in this pathology.

Material and Methods

Ninety-seven premature newborns, hospitalized in our NICU between January 1995 and January 1997 with a birth weight of less than 2500 g were examined systematically with cranial ultrasonography (CU). Standard coronal and parasagittal images were performed with Pie Medical (Holland) equipment with 5 MHz transducer. Intracranial hemorrhage is recognized by one or more of the following features: echogenic intra-parenchymal mass, unilateral or bilateral ventriculomegaly with intraventricular hyperechongenic clot and periventricular germinal matrix hyperechogenicity. χ^2 test was used to show the relation between IVH and risk factors like low birth weight, intrauterine growth retardation, low gestational age, type of delivery, artificial ventilation, necrotizing enterocolitis, patent ductus arteriosus, sepsis, thrombocytopenia ($< 50,000/mm^3$), hypoglycemia, (< 40 mg/dl), hypercarbia ($pCO2 < 60$ torr), fresh frozen plasma (FFP) infusion, hypotension (< 50 mmHg in term; < 40 mmHg in preterm newborns), and hypertension (> 90 mmHg in term; > 80 mmHg in preterm newborns). Values are expressed as mean ± standard deviation and $p < 0.05$ denotes a statistically significant difference between groups.

Results

Mean birth weight of this population was 1540 ± 430 g (720-2450), gestational age 31.6 ± 2.4 weeks (26-37), first minute Apgar score 5 ± 2 (0-9). Most of the cerebral ultrasonographic scans (64%) are done in the first seven days and mean age at the first CU is 7.9 days. In this population of 97 newborns, IVH is diagnosed in 40 of them (41%) and its classification as a function of severity is shown in Table I. Incidence of IVH as a function of birth weight is listed in Table II and statistical relations between IVH and risk factors are shown in Table III. Incidence of IVH is statistically more significant in newborns with a gestational age of less than 33 weeks, having artifical ventilation and infusion of FFP.

Table I: Classification of IVH in Function of its Severity

	NICU of Cerrahpaşa University Hospital		Volpe[5]
Grade I	6	15%	35%
Grade II	20	50%	40%
Grade III	14	35%	25%
IVH + periventricular hemorrhagic infarction	7	17%	15%
Total	40		

Table II: IVH Cases Classified in Function of Birth Weight

	IVH +	IVH –	Total
500-1000 g	6 (50%)	6 (50%)	12
1001-1500 g	19 (54%)	16 (46%)	35
1501-2000 g	10 (30%)	23 (70%)	33
2001-2500 g	5 (29%)	12 (71%)	17

Table III: Risk Factors and IVH Incidence

		Presence of Intraventricular Hemorrhage		
Risk Factors		(+)	(–)	P
Intrauterine growth	SGA	8 (50%)	8 (50%)	NS
	SGA	32 (40%)	49 (60%)	
Delivery	vaginal	20 (43%)	26 (57%)	NS
	cesarean section	20 (39%)	31 (61%)	
Gestational age	< 33 weeks	35 (55%)	29 (45%)	< 0.0005
	≥ 33 weeks	5 (15%)	28 (85%)	
Birth weight	≤ 1500 g	25 (53%)	22 (47%)	< 0.05
	> 1500 g	15 (30%)	35 (70%)	
Surfactant application	+	9 (64%)	5 (36%)	NS
	–	31 (37%)	52 (63%)	
Artifical ventilation	+	32 (52%)	29 (48%)	< 0.01
	–	8 (22%)	28 (78%)	
Sepsis	+	18 (51%)	17 (49%)	NS
	–	22 (35%)	40 (65%)	
Clinical PDA	+	4 (33%)	8 (67%)	NS
	–	36 (42%)	49 (58%)	
NEC	+	1 (100%)	0	NS
	–	39 (41%)	57 (59%)	
Thrombocytopenia	+	3 (50%)	3 (50%)	NS
	–	37 (41%)	54 (59%)	
Hypoglycemia	+	11 (55%)	9 (45%)	NS
	–	29 (38%)	48 (62%)	
Hypercarbia	+	10 (45%)	12 (55%)	NS
	–	30 (40%)	45 (60%)	
Infusion of FFP	+	28 (52%)	26 (48%)	< 0.05
	–	12 (28%)	31 (72%)	
Hypotension	+	9 (47%)	10 (53%)	NS
	–	31 (40%)	47 (60%)	
Hypertension	+	13 (57%)	10 (43%)	NS
	–	27 (36%)	47 (64%)	

SGA : small for gestational age. AGA : appropriate for gestational age.
PDA : patent ductus arteriosus. NEC : necrotizing enterocolitis.
FFP : fresh frozen plasma.

Discussion

In the NICU of the University Hospital of Cerrahpaşa, IVH incidence was found to be 41 percent. This number is similar to those presented in the literature in the late 1970's and early 1980's. Distribution of our newborns with IVH in function of severity (Table I) is different from those of Volpe[5]; in particular, the incidences of IVH with grade II and III are higher than the results of Volpe. When we compare our IVH incidence in function of birth weight (Table II) with the results of Perlman[4], we find that they are 50 and 51 percent, respectively, between 500-1000 g; 54 and 17 percent, respectively, between 1001-1500 g; and 30 and 15 percent, respectively, between 1501-2000 g. Although these differences can be explained by the small number of our population, it is also related to the pre- and postnatal conditions of the two populations. Technological advances, better understanding of neonatal problems, and increased numbers of trained medical staff decreased the incidence of IVH to 20 percent in the early 1990's. We think that we also will be able to decrease our IVH incidence with better pre- and postnatal care.

As already shown in anatomic studies, the capillary bed becomes more mature and the subependymal germinal matrix, which is the most susceptible region to IVH, undergoes a progressive decrease in size from a width of 2.5 mm at 24 weeks to 1.4 mm at 32 weeks[7]. It was not suprising for us to find a statistically significant difference of IVH incidence between infants born before and after 33 weeks of gestational age. On the other hand, when only birth weight is considered, there is no statistically significant difference.

Kuban et al.[8] showed in their study that premature small-for-gestational-age (SGA) infants of toxemic mothers had a reduced incidence of germinal matrix hemorrhage because these infants exhibit an accelerated maturation of the brain. In our population, the risk of IVH was not different between SGA and appropriate-for-gestational-age (AGA) infants.

It has been widely discussed whether abdominal delivery reduces the risk of IVH. Leviton et al.[9] showed that infants delivered vaginally were more likely to develop IVH than those delivered abdominally. We could not show a statistically significant relation between the mode of delivery and IVH, but we did find that 43 percent of newborns with vaginal delivery presented an IVH in contrast to only 39 percent of cases with abdominal delivery.

The role of coagulopathy as a cause of IVH is not very clear. Though administration of FFP is shown to decrease the incidence of IVH[10] without any amelioration of coagulation parameters, in our population, the risk of IVH is higher for infants who have received it. In a study where an experimental group receiving two doses of coagulation factor concentrate was compared to a control group,

IVH was more frequent in treated infants[11]. These results, which are similar to ours, may be explained by the increased blood flow of germinal matrix secondary to increased arterial blood pressure after FFP administration.

Artifical ventilation along with high inspiratory positive pressure, tracheal aspiration and complications increase cerebral venous pressure or cause fluctuating cerebral blood flow velocity, both of which are known to be important factors of IVH[12]. Another study[13] showed that there was a significant decrease in fluctuating cerebral blood flow from the first day of life to 72 hours of age between ventilated infants paralyzed by pancuronium bromide and those that are nonparalyzed. Our results are consistent with those of Perlman et al.[13] because we also found higher IVH incidence in ventilated premature infants. None of our patients was paralyzed.

It is now almost evident that surfactant treatment reduces mortality and pulmonary complications in preterm infants with respiratory distress syndrome. On the other hand, Horbar et al.[14] showed in a large multicenter study that infants receiving bovine surfactant had an increased number of severe periventricular hemorrhages compared with the control group. Cowan et al.[15] tried to show physiological changes after surfactant administration and found a 15 percent fall in mean airway pressure and a 36 percent fall in cerebral blood flow velocity. They concluded that these acute changes may increase the risk of IVH. Even though the difference was not significant, we also found that infants receiving surfactant had a greater incidence of IVH (9/14) than the ones who were not treated (31/83).

The role of hypoglycemia in the pathogenesis of IVH is not clear, but Pryds et al.[16] showed that it increased cerebral blood flow which might contribute to IVH. In our group of patients, hypoglycemia was not a significant risk factor of IVH.

Hypercarbia is also considered as a risk factor in IVH. Greisen et al.[17] showed that in a group of ventilated preterm infants an important reactivity of cerebral blood flow to changes in $PaCO_2$ existed. In another large study[18], hypercarbia, defined as $PaCO_2$ greater than 60 mmHg, showed a positive relation with IVH. We could not find a significant difference for IVH between infants with or without a hypercarbia episode.

Arterial hypertension is shown to have a potential role in the subquent occurrence of IVH[19]. In our study, presence of hypertension increased the risk of IVH, but this was not statistically significant probably because of the small number of the population.

We believe that we will be able to decrease our IVH rate with improvements in our pre- and postnatal care of newborns.

REFERENCES

1. Papile LA, Burnstein J, Burnstein R, Koffler H. Incidence and evolution of subependymal and intraventricular hemorrhage: a study of infants with birth weights less than 1500 g. J Pediatr 1978; 92: 529-534.
2. Levene MI, Wigglesworth JS, Dubowitz V. Cerebral structure and intraventricular haemorrhage in the neonate: a real time ultrasound study. Arch Dis Child 1981; 56: 416-424.
3. Philip AG, Allan WC, Tito AM, Wheeler LR. Intraventricular hemorrhage in preterm infants: declining incidence in the 1980s. Pediatrics 1989; 84: 797-801.
4. Perlman JM, Volpe JJ. Intraventricular hemorrhage in extremely small premature infants. Am J Dis Child 1986; 140: 1122-1124.
5. Volpe JJ. Neurology of the Newborn (3rd ed).. Philadelphia: W.B. Saunders Company; 1995: 424-425.
6. Hope PL, Gould Sj, Howard S, Hamilton PA, Cóstello AM, Reynolds EO. Precision of ultrasound diagnosis of pathologically verified lesions in the brains of very preterm infants. Dev Med Child Neurol 1988; 30: 457-471.
7. Szymonowicz W, Schafler K, Cussen LJ, Yu VY. Ultrasound and necropsy study of periventricular haemorrhage in preterm infants. Arch Dis Child 1984; 59: 637-642.
8. Kuban KC, Leviton A, Pagano M, et al. Maternal toxemia is associated with reduced incidence of germinal matrix hemorrhage in premature babies. J Child Neurol 1992; 7: 70-76.
9. Leviton A, Fenton T, Kuban KC, Pagano M. Labor and delivery characteristics and the risk of germinal matrix hemorrhage in low birth weight infants. J Child Neurol 1991; 6: 35-40.
10. Beverly DW, Pitts-Tucker TJ, Congdon PJ, Arthur RJ, Tate G. Prevention of intraventricular haemorrhage by fresh frozen plasma. Arch Dis Child 1985; 60: 710-713.
11. Horbar JD. Prevention of periventricular-intraventricular hemorrhage. In: Sinclair JC, Bracken MB (eds). Effective Care of the Newborn Infant. Oxford: Oxford University Press; 1992: 562-590.
12. Perlman JM, McMenamin JB, Volpe JJ. Fluctuating cerebral blood-flow velocity in respiratory-distress syndrome. Relation to the development of intraventricular hemorrhage. N Engl J Med 1983; 309: 204-209.
13. Perlmana JM, Goodman S, Kreusser KL, Volpe JJ. Reduction in intraventricular hemorrhage by elimination of fluctuating cerebral blood-flow velocity in preterm infants with respiratory distress syndrome. N Engl J Med 1985; 312: 1353-1357.
14. Horbarr JD, Soll RF, Schachinger H, et al. A European multicenter randomized controlled trial of single dose surfactant therapy for idiopathic respiratory distress syndrome. Eur J Pediatr 1990; 149: 416-423.
15. Cowan F, Whitelaw A, Wertheim D, Silverman M. Cerebral blood flow velocity changes after rapid administration of surfactant. Arch Dis Child 1991; 66: 1105-1109.
16. Pryds O, Christensen NJ, Friis-Hansen B. Increased cerebral blood flow and plasma epinephrine in hypoglycemic, preterm neonates. Pediatrics 1990; 85: 172-176.
17. Greisen G, Trojaborg W. Cerebral blood flow, $PaCO_2$ changes, and visual evoked potentials in mechanically ventilated, preterm infants, Acta Paediatr Scand 1987; 76: 394-400.
18. Wallin LA, Rosenfeld CR, Laptook AR, et al. Neonatal intracranial hemorrhage: II. Risk factor analysis in an inborn population. Early Hum Dev 1990; 23: 129-137.
19. Perry EH, Bada HS, Ray JD, Korones SB, Arheart K, Magill HL. Blood pressure increases, birth weight-dependent stability boundary, and intraventricular hemorrhage. Pediatrics 1990; 85: 727-732.