THE EFFECTS OF ANTENATAL CORTICOSTEROID TREATMENT ON IVH-PVH OF PREMATURE INFANTS

Hajrija Maksić[1]*, Feriha Hadžagić-Ćatibušić[1], Suada Heljić[1], Jadranka Dizdarević[2]

[1] Pediatric Clinic, University of Sarajevo Clinics Centre, Bolnička 25, 71000 Sarajevo, Bosnia and Herzegovina

2 Gynecology and Obstetrics Clinic, University of Sarajevo Clinics Centre, Bolnička 10, 71000 Sarajevo, Bosnia and Herzegovina

* Corresponding author

Abstract

Intraventricular-periventricular hemorrhage (IVH-PVH) is the most frequent type of intracranial hemorrhage in premature infants and the major cause of neurodevelopmental disabilities in children too.
The objective of this work is to evaluate the effects of prenatal corticosteroid treatment on the incidence of IVH-PVH in premature infants.
The study enrolled 163 prematures of 26-34 weeks' gestation. They have been divided into two groups: the experimental group (80/163), who have been treated with corticosteroids prenatally and control group (83/163), who have not received such treatment.
There is statistically significant difference in IVH-PVH incidence between the experimental group (18/80) and control group (32/83) (χ^2 =5,616, p<0,05).
There is no statistically significant difference in Apgar score after 5 minutes between the experimental group and control group of IVH-PVH prematures, t= 0,121.
There is no statistically significant difference in mean gestation age between the experimental group (30,74 weeks) and control group (29,97 weeks) of IVH-PVH prematures, t= 1,299.
There is no statistically significant difference in mean birth weight between the experimental group (1479,44 grams) and control group (1379,37 grams) of IVH-PVH prematures, t= 0,913.
Antenatal corticosteroid treatment of premature infants reduced the incidence of IVH-PVH significantly.
There is no statistically significant difference in Apgar score after 5 minutes, mean gestation age and mean birth weight between the experimental and control group of IVH PVH prematures.

KEY WORDS: IVH-PVH, antenatal corticosteroid treatment

Introduction

Intra-periventricular hemorrhage (IVH-PVH) is the most frequent type of intracranial hemorrhage in prematures. It is also the major cause of neurodevelopmental disabilities in prematures. Factors predisposing to IVH-PVH are: prematurity, respiratory distress syndrome (RDS), hypoxic-ischemic lesions, reperfusion, lesions of the blood vessels, disturbances of the cerebral blood flow, pneumothorax, hypovolaemia and hypertension (1). These factors cause rupture in the blood vessels of the germinal matrix, where the initial location of intracranial bleeding for prematures is. 80% of these patients develop hemorrhage into the ventricles and 10-15% patients develop hemorrhage into periventricular regions (2). In the most cases, IVH is followed by acute dilatation of the ventricles. 10-15% infants with low birth weight develop hydrocephalus, which is stable in 65% cases. Progressive hydrocephalus, with ventriculoperitoneal shunt and intraparenchimal hemorrhage is associated with unfavorable neurodevelopmental outcome. IVH with intraparenchimal echogenicity above 1 cm is associated with high rate of mortality and high risk of motor and cognitive disabilities. If the IVH grade I and grade II are not associated with periventricular leukomalatia (PVL) and intraparenchimal bleeding, they carry lower risk of long-term neurodevelopmental sequels. Corticosteroids administered to pregnant women who are at high risk of preterm labor have reduced the incidence of RDS, IVH and neonatal mortality. They are administered in the cases when the delivery is expected before 34 weeks of gestation. Dexamethason is recommended prenatally in a dose of 4x6 mg, each 12 hours and betamethason 2x12 mg, once a day („single course of antenatal corticosteroids"). The favorable outcome is expected if the delivery happens in the interval between 24 hours and 7 days, maximum 10 days after the administration of corticosteroids (3, 4, 5). If the delivery does not happen in this interval, there is no need to repeat prenatal treatment with corticosteroids, because there are some indications of increased incidence of severe types of IVH-PVH and neurodevelopmental disabilities.

Patients and Methods

The study has included 163 prematures with gestation age 26-34 weeks. The patients have been divided into two groups: experimental group (80/163), with patients who were treated with dexamethason prenatally, and control group (83/163), with patients who did not receive such treatment. In the experimental group, all the patients were treated with "single course" dexamethason. The study has not included prematures born before 26 and after complete 34 weeks of gestation, prematures with intrauterine growth retardation (IUGR), prematures whose mothers suffered from tuberculosis, gastric or duodenal ulcer or diabetes and prematures with congenital malformations. In all cases the bleeding was diagnosed by ultrasound and documented by neurosonograms.

Papile has classified IVH-PVH:

Grade I: bleeding into the germinal matrix

Grade II: the blood is in the lateral ventricles, but they are not dilated

Grade III: the blood is in the lateral ventricles and they are dilated

Grade IV: bleeding into the lateral ventricles, with intraparenchimal hemorrhage

Results

IVH-PVH	Number of patients	%
EXPERIMENTAL GROUP		
IVH-PVH grade I+II	15	18,75
IVH-PVH grade III+IV	3	3,75
Total IVH-PVH	18	22,50
Without IVH-PVH	62	77,50
Total	80	100,00
CONTROL GROUP		
IVH-PVH grade I+II	12	14,50
IVH-PVH grade III+IV	20	24,00
Total IVH-PVH	32	38,50
Without IVH-PVH	51	61,50
Total	83	100,00

TABLE 1. The incidence of IVH-PVH in the experimental and control group

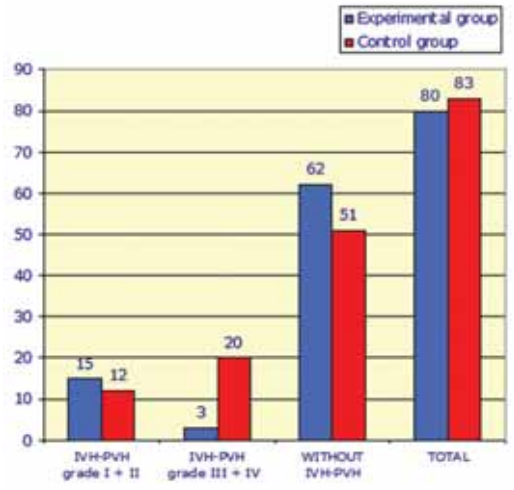

FIGURE 1. The incidence of IVH-PVH in the experimental and control group

The incidence of IVH-PVH is significantly lower in the experimental, corticosteroid group (18/80) in comparison to control group (32/83) (χ^2 =5,616 p<0,05)
The percentage of severe forms of IVH-PVH is significantly higher in the control group (24%), while its percentage in the experimental group is 3,75%.

IVH-PVH	Number of patients (n)	Mean value of Apgar score (x)	Standard deviation SD
EXPERIMENTAL GROUP			
IVH-PVH grade I+II	15	6,86	1,92
IVH-PVH grade III+IV	3	3,75	4,94
Total IVH-PVH	18	6,17	3,16
Without IVH-PVH	56	8,02	0,84
Total	74	6,99	2,35
CONTROL GROUP			
IVH-PVH grade I+II	12	6,45	1,78
IVH-PVH grade III+IV	20	5,84	1,23
Total IVH-PVH	32	6,06	1,92
Without IVH-PVH	49	7,21	1,64
Total	81	6,00	2,27

TABLE 2. IVH-PVH in relation to the mean value of Apgar score

Apgar score is missing for six patients from control and two patients from the experimental group. Patients with IVH-PVH in the control and experimental group have significantly lower mean value of Apgar score in comparison to the patients without IVH-PVH (experimental group t=7,503, p<0,001, control group t=2,735, p <0,01). But, there is no statistically significant difference of the mean value of Apgar score between the corticosteroid group and control group of prematures with IVH-PVH (t=0,121).

		Experimental group	Control group
Patients with IVH-PVH	n	18	32
	x	1479,44	1379,37
	SD	390,64	336,28
Patients without IVH-PVH	n	62	51
	x	1975,17	1738,67
	SD	463,70	457,60

TABLE 3. The mean birth weight in relation to IVH-PVH (experimental and control group)

The mean birth weight of patients with IVH-PVH in both groups is significantly lower in comparison to the mean birth weight of patients without IVH-PVH, as it is expected. (Patients with IVH-PVH: t= 0,913, patients without IVH-PVH: t=2,718). But, there is no statistically significant difference in the mean birth weight between experimental and control group of prematures with IVH-PVH.

		Experimental group	Control group
Patients with IVH-PVH	n	18	32
	x	30,74	29,97
	SD	2,05	1,94
Patients without IVH-PVH	n	62	51
	x	32,30	31,58
	SD	1,34	1,85

TABLE 3. The mean birth weight in relation to IVH-PVH (experimental and control group)

There is no statistically significant difference in the mean gestation age between experimental and control group of prematures with IVH-PVH.
There is no statistically significant difference in the sex distribution between experimental and control group of the prematures with/without IVH-PVH (χ^2 test for experimental group 0,307 – not significant, χ^2 test for control group 0,011-not significant)

Discussion

The incidence of IVH-PVH has been lower in recent years, but higher survival rate of infants with low birth weight indicates that occurrence of these lesions remained an important problem. Their prevention has special importance, since the incidence of long-term neurological sequels in relation to the grade of bleeding classified by Papile is: 15% - 30% - 40% - 90% (6, 7). The favorable effect of corticosteroid treatment on the maturation of a fetus in risk of premature labor has been known since 1972, from the studies of Ligins and coworkers. The official recommendation for its application was given by American Institute for Health, in 1994, after the analysis of all published articles confirmed the reduction of RDS and IVH-PVH incidence and lower rate of neonatal mortality. The effect of corticosteroids on fetal brain is not clear enough, but it is well known that favorable effects of antenatal corticosteroid treatment on IVH-PVH have incomplete correlation with the improvement of pulmonal morbidity. Probably, those favorable effects were the consequence of cerebral blood flow stabilization and steroid induced maturation of vascular structures in germinal matrix. All patients enrolled in our study were treated with single course of dexamethason. Randomized control studies focused on the effect of corticosteroid treatment on the brain and neurodevelopment failed to prove neurological defects in the age of 6, 12 and 20 years of life (8,9,10). These studies have also included the aspect of the social, emotional and sexual development. Only the study of Mac Arthur and coworkers has found some subtle neuro-

IVH-PVH	Male		Female		Total	
	n	%	n	%	n	%
Experimental group	15	6,86	1,92			
With IVH-PVH grade I + II	9	18,8	6	18,7	15	18,8
With IVH-PVH grade III + IV	3	6,2	-	-	3	3,7
Total with IVH-PVH	12	25,0	6	18,7	18	22,5
Total without IVH-PVH	36	75,0	26	81,3	62	77,5
TOTAL	48	100,0	32	100,0	80	100,0
Control group						
With IVH-PVH grade I + II	6	11,8	6	18,8	12	14,5
Without IVH-PVH grade III + IV	14	27,4	6	18,8	20	24,1
Total with IVH-PVH	20	39,2	12	37,6	32	38,6
Total without IVH-PVH	31	60,8	20	62,4	51	41,4
TOTAL	51	100,0	32	100,0	83	100,0

TABLE 5. Sex distribution of the patients with/without IVH-PVH (experimental and control group)

logical defects, i.e. the lesion of visual memory (11). In our study, we have found that prenatal treatment with corticosteroids has reduced IVH-PVH in prematures significantly, mostly bleeding grade III and IV classified by Papile. In the corticosteroid, experimental group 18,75% (15/80) infants developed intracranial bleeding grade I and grade II, while 3,75% (3/80) infants developed intracranial bleeding grade III and grade IV. In the control group 14,5 % (12/83) infants developed intracranial bleeding grade I and grade II, while 24% (20/83) infants developed intracranial bleeding grade III and grade IV. According to the literature, 13 studies including 2 872 infants, showed that antenatal corticosteroid treatment was associated with the reduction of intracranial hemorrhage (relative risk RR 0,54; 95% confidence interval 0,43-0,69). It was also confirmed that antenatal corticosteroids did not increase the risk of puerperal sepsis, chorioamnionitis and maternal death (12). Reports exist that indicate that combination of prenatal corticosteroids and vitamin K (dexamethason 10 mg a day, plus vitamin K 10 mg a day, 2-7 days) may significantly reduce the incidence of severe forms of IVH-PVH (13). IVH-PVH, together with periventricular leucomalatia and cerebral infarcts constitute the most frequent causes of cerebral palsy in children with small birth weight (14). IVH-PVH is a typical for prematures bellow 35 weeks of gestation. According to the reports from 80-ies, the incidence of IVH-PVH in prematures with birth weight bellow 1500 grams was about 35-50%, but in later reports the incidence dropped to 15-30%. In our study, there is no statistically significant difference in mean birth weight, mean gestation age and mean value of Apgar score after 5 minutes between experimental and control group of prematures with IVH-PVH. This fact has confirmed the clinical practice up to now that low gestation age, small birth weight and perinatal asphyxia are important risk factors for development of IVH-PVH, regardless of prenatal treatment with corticosteroids. Martin Fernandez and coworkers compared two groups of prematures with IVH, in relation to the survival. The first group included prematures that survived and the second group included prematures that did not survive. The results of the study emphasized that lower gestation age, lower birth weight, mechanical ventilation and IVH grade IV, influence mortality rate of newborns with IVH (15). Majeda and coworkers analyzed perinatal risk factors for development of high grades of IVH-PVH in infants with low birth weight and RDS. They found that antenatal treatment with corticosteroids has significantly reduced the incidence of all types of intracranial bleeding, while the PDA and pneumothorax have increased its incidence (16). In our study, we have compared the effects of corticosteroid treatment between experimental and control group of prematures without intracranial hemorrhage and we have found statistically significant difference in mean birth weight and mean gestation age. We have explained these data as a consequence of better perinatal control of prematures in the experimental group (regular medical controls, timely hospitalization of pregnant women when if necessary). The prematures in the control group have been born unexpected, with sudden premature labor.

Conclusion

Antenatal corticosteroid treatment ("single course") of prematures has significantly reduced the incidence of IVH-PVH and should become routine clinical practice. But, low birth weight and lower gestation age have remained important risk factors for the development of IVH-PVH. It is necessary to continue the efforts on prevention of prematurity.
Since IVH takes important part of neonatal mortality and represents important predictive factor for neurodevelopment, the reduction of its incidence is as important as reduction of RDS.

List of Abbreviations

IVH-PVH	-	intra-periventricular hemorrhage
RDS	-	respiratory distress syndrome
PVL	-	periventricular leukomalatia
IUGR	-	intrauterine growth retardation

References

(1) Behrman R. E., Kliegman R.M., Jenson H.B. Nelson textbook of pediatrics – 17th ed. 2003 WB Saunders Co.

(2) Fanarhof A.A., Martin R.J. Neonatal – perinatal medicine: diseases of the fetus and infant 6th ed. Philadelphia Lippincott-Raven1997; pp. 264-284

(3) NIH Consensus Developmental Conference. Am. J. Obstet. Gynecol. 1995; 173:146-152

(4) Clemnts J.A. Function of the alveolar lining. Am. Rev. Respir. Dis. 1977;115: 67-71

(5) Robertson B. Pathology and pathophysiology of neonatal surfactant deficiency. In: Robertson , B., et al editors: Pulmonary Surfactant, Amsterdam, Elsevier Science Publisher, 1984.; 126-138

(6) Pilip A.G.S., Allan W.C., Tito A.M. at al. Intraventricular hemorrhage: declining incidence in the 1980s. Pediatrics 1989; 84: 797-801

(7) Volpe J.J. Intraventricular hemorrhage and brain injury the premature infant: Neuropatology end Pathogenesis. Clinics in Perinatology 1989; 16: 341-411

(8) Bunt J.E., Carnielli VP., Darcos Wattimena JL. et al. The effect in premature infants of prenatal corticosteroids on endogeneus surfactant synthesis as measured with stable isotopes. Am. J. Respir. Crit. Care Med. 2000;162:844-849

(9) Smolders-De Haas H., Neuvel J., Schmand B. et al. Physical development and medical history of children who were treated antenatally with corticosteroids to prevent respiratory distress syndrome: a 10 to 12 year follow-up. Pediatrics 1990;86:65-70

(10) French N.P., Hagan R., Evans S.F., et al. Repeated antenatal corticosteroids: size at birth and subsequent development. Am. J. Obstet. Ginecol. 1999;180: 114-121

(11) Derks J.B., Guissani D.A., Jenkins S.L. et al. A comparative study of cardiovascular, endocrine and behavioral effects of betamethasone and dexamethasone administration of fetal sheep. J. Physiol. 1997; 499: 217-226

(12) Neilson J.P. Cocharne update: antenatal corticosteroids for accelerating fetal lung maturation for women at risk of preterm birth. Obstet. Gynecol. 2007 ;109(1):189-190

(13) Liu J., Wang Q., Zhao J.H., Chen Y.H., Qin G.L. The combined antenatal corticostereoids and vitamin K therapy for preventing periventricular-intraventricular hemorrhage in premature newborns less then 35 weeks gestation. J. Trop. Pediatr. 2006 ;52(5):355-359

(14) Meberg A., Broch H. Etiology of cerebral palsy. J. Perinat. Med. 2004;32(5):434-439

(15) Martin Fernandez-Mayorales Daniel, Munoz Jareno Nuria, Martin Caballero Jose Manuel. Intraventricular hemorrhage: differences between surviving and no surviving newborns. The J of Maternal-Fetal & neonatal Medicine 2004;16 (Suppl I):288

(16) Hammoud M.S. at al: Perinatal events and the risk of severe intraventricular hemorrhage in low birth weight infants. A prospective study. J. Perinat. Med. 2005; 33 (Suppl.1): 117