Institute of Child and Youth Healthcare of Vojvodina, Novi Sad

Originalni naučni rad
Original study
UDK 616.831-005.1-053.32
DOI: DOI:10.2298/MPNS1008454S

INTRACRANIAL HAEMORRHAGE AFTER TRANSPORT OF PREMATURE NEWBORNS

INTRAKRANIJALNO KRVARENJE I TRANSPORT „K SEBI” PREVREMENO ROĐENOG NOVOROĐENČETA

Slobodan SPASOJEVIĆ, Vesna STOJANOVIĆ, Radojica SAVIĆ i Aleksandra DORONJSKI

Summary – Intracranial hemorrhage remains an important factor of premature newborns' morbidity. Its incidence is significantly influenced by adequate perinatal care and safe neonatal transport. Risk factors for the development of intracranial hemorrhage in premature newborns after neonatal transport were analyzed in the retrospective transversal clinical study. Out of 150 study subjects, 60% (n=90/150) had intracranial hemorrhage with a statistically significant difference in relation to Apgar score, gestational age, birth weight, age at the moment of transport and the prophylactic use of surfactant. In this group, grades I/II intracranial hemorrhage were detected in 77% (n=69/90), while grades III/IV intracranial hemorrhage were diagnosed in 23% (n=21/90). A statistically significant difference was observed in relation to gestational age, birth weight, antenatal use of tocolytics and steroids, delivery mode and age in the time of transport between these groups. All patients were transferred to Intensive Care Unit, the duration of transport was less than 5 minutes in 71% 9n=107/150), whereas longer transport was recorded in 29% (n=43/150). In the group of longer transport, prophylactic surfactant was less frequently used with a higher incidence of grades III/IV intracranial hemorrhage. In order to prevent the development of intracranial hemorrhage in premature newborns, the most important measures are the antenatal use of steroids and postnatal prophylactic use of surfactant.

Key words: Intracranial Hemorrhages; Transportation of Patients; Infant, Premature; Risk Factors; Perinatal Care; Adrenal Cortex Hormones; Pulmonary Surfactants + therapeutic use

Introduction

Advances in perinatal medicine and especially regionalization of perinatal care have led to a significant decline of perinatal mortality during the last two decades. Perinatal regionalization integrates regional maternity wards with tertiary perinatal centre that has neonatal intensive care unit in order to provide adequate perinatal care to high-risk pregnant women and their newborns [1]. Previous studies have shown that antenatal transfer in utero [1,2] and delivery in the tertiary perinatal centre [3,4] significantly contribute to a mortality decline of very low birth weight (VLBW) premature newborns. On the other hand, simultaneously with increased number of perinatologists and neonatologists in the healthcare system, an issue of deregionalization of perinatal care has reemerged.

Concomitantly with a decline in perinatal mortality, attention has been directed more toward morbidity of premature newborns as well as short- and long-term consequences of their treatment. Despite the decline in incidence from 40-50% [5] to approximately 20% [6], intracranial hemorrhage (ICH), especially grades III and IV, remains a significant factor in morbidity of VLBW premature newborns with long-term neurological consequences in more than 35% of affected patients [7]. The exact pathway of ICH is not completely known. It is probably multifactorial, with significant contribution of prenatal, intrapartal and postnatal factors. Therefore, it is likely that adequate perinatal care, place of birth and transport of premature newborns to a tertiary perinatal centre influence the incidence of ICH.

The aim of this study was to analyze the incidence of ICH and its risk factors in premature newborns transferred after birth and treated at the Intensive Care Unit (ICU), Department of Neonatology and Intensive Care, Pediatric Clinic, Institute of Child and Youth Healthcare of Vojvodina, Novi Sad between March 2007 and October 2008.

Material and methods

A retrospective study included history charts of 150 premature newborns transferred postnatally and treated at the ICU, Department of Neonatology and Intensive Care, Pediatric Clinic, Institute of Child and Youth Healthcare of Vojvodina, Novi Sad.

The inclusion criteria were as following: premature birth (gestational age (GA) less than 37-weeks` gestation (gw), clinical and radiological signs of respiratory distress syndrome (RDS), admission at the ICU and brain ultrasound in the first 48 hours of life. All patients were transferred postnatally from local (Novi Sad) and regional maternity wards (Subotica, Sombor, Vrbas, Senta, Zrenjanin, Sremska Mitrovica) to the ICU. Newborns with major congenital anomalies were excluded from the study. The following parameters were analyzed: conceiving mode (spontaneous, in vitro fertilization), antenatal use of tocolytics and/or steroids, delivery mode (vaginal, Caesarian section), gender, Apgar score at 5th minute (AS 5. min), gestational age, birth weight (BW), prophylactic and/or therapeutic use of sur-

Corresponding Author: Asist. mr sc. med. Slobodan Spasojević, Institut za zdravstvenu zaštitu dece i omladine Vojvodine, 21000 Novi Sad, Hajduk Veljkova 10, E-mail: sspas@ptt.rs

Abbreviations

VLBW – very low birth weight
IL – interleukin
CH – intracrnial hemorrhage
BW – birth weight
GA – gestational age
GW – gestation week
RDS – respiratory distress syndrome
AS 5. min. – Apgar score at 5 mun
ICH – intracranial haemorrhage
ICU – intesive care unit

factant, age (in hours of life) at the admission and duration of performed neonatal transport.

The prophylactic use of surfactant meant intratracheal instillation at birth (before first spontaneous breaths or more often after initial resuscitation but within the first 10-30 minutes of life). The therapeutic use of surfactant meant its application in the case of developed clinical and radiological signs of RDS either in the first 2 hours of life (early application) or after this time-frame (late application). Natural porcine surfactant (poractant-alpha, Curosurf®) was used in the dosage of 100 milligrams per kilogram BW.

Brain ultrasound was performed at the admission (1st day of life), on the 3rd and 7th day of life, and once per week or according to indications afterwards. The classification of ICH according to Volpe et al. was used [8]:

Grade I – germinal matrix hemorrhage-intraventricular hemorrhage (GMH-IVH)

Grade II – intraventricular hemorrhage without ventricular dilatation

Grade III – intraventricular hemorrhage with acute ventricular dilatation (clots within more than 50% of ventricles)

Grade IV – intraparenchimal lesion

Student T-test and Hi square test were used for statistical analysis and p values < 0.05 were considered as statistically significant.

Results

Among 150 premature newborns, 60% (n=90/150) were diagnosed with ICH.

General demographic characteristics of the group are shown in **Table 1**. Among premature newborns diagnosed with ICH, 77% (n=69/90) had grade I/II and 23% (n=21/90) had grade III/IV.

Characteristics of premature newborns with ICH grades I/II and III/IV are shown in **Table 2**.

All of examinees were transferred postnatally to the ICU; 71% of them (n=107/150) were transported from the local maternity ward (duration of transport approximately 5 minutes) and 29% (n=43/150) from regional maternity wards (average duration of transport 72.5 minutes).

Characteristics of premature newborns from shorter and longer neonatal transport are shown in **Table 3**.

Multifactor logistic regression analysis was performed in order to predict the grade of ICH.

Table 1. Characteristics of premature newborns with and without ICH

Tabela 1. *Karakteristike prevremeno rođene novorođenčadi sa i bez IKH*

	IKH +(n=90) *ICH +(n=90)*	IKH - (n=60) *ICH - (n=60)*	p
AS 5. min.	6,34	7	p<0,05*
GS GA/*GN GW*	29,2	33,1	p<0,05*
PTM (g)/*BW (g)*	1286,9	2015	p<0,05*
In vitro fertilizacija *In vitro fertilization*	15/90 (17%)	5/60 (8%)	p>0,05
Tokolitici/*Tocolytics*	11/90 (12%)	8/60 (13%)	p>0,05
Kortikosteroid antenatalno *Antenatal steroids*	33/90 (37%)	17/60 (28%)	p>0,05
Vaginalni porođaj/*Vaginal delivery*	41/90 (45%)	26/60 (43%)	p>0,05
Carski rez/*Cesarian section*	49/90 (55%)	34/60 (57%)	p>0,05
Uzrast u vreme transporta (h) *Age at the beginning of transport (h)*	7,35	12,2	p<0,05*
Dužina transporta (min) *Transport duration (min)*	24,3	27	p>0,05
Surfaktant preventivno *Prophylactic surfactant*	53/90 (59%)	19/60 (32%)	p<0,05*
Surfaktant terapijski *Therapeutic surfactant*	28/90 (31%)	24/60 (40%)	p>0,05

ICH was the dependent variable with binary outcome (1 - grades I/II ICH; 2 – grades III/IV ICH). Independent variables were the following: 1) x_1=antenatal steroids; 2) x_2=gestational age; x_3=caesarean section; x_4=age at the start of neonatal transport (in hours). The equation of logistic regression curve was: $p=(1+\exp(-b_0 - b_1x_1 - b_2x_2 - b_3x_3 - b_4x_4))^{-1}$. Values of b_i were determined by quazi-Newton method: b_0=14, b_1=-2,13879, b_2=-0,46242, b_3= -2,51056, b_4= -0,067.

Table 2. Characteristics of premature newborns with grades I/II and grades III/IV ICH

Tabela 2. *Karakteristike prevremeno rođene novorođenčadi sa IKH I/II i III/IV stepena*

	IKH I/II°(n=69) *ICH I/II°(n=69)*	IKH III/IV°(n=21) *ICH III/IV°(n=21)*	p
AS 5. min.	6,62	6,04	p>0,05
GS GA/*GN GW*	30,85	27,6	p<0,05*
PTM (g)/*BW (g)*	1548	1025	p<0,05*
In vitro fertilizacija *In vitro fertilization*	13/69 (19%)	2/21 (9%)	p>0,05
Tokolitici/*Tocolytics*	6/69 (13%)	2/21 (9%)	p<0,05*
Kortikosteroid antenatalno *Antenatal steroids*	30/69 (43%)	3/21 (14%)	p<0,05*
Vaginalni porođaj *Vaginal delivery*	30/69 (44%)	19/21 (91%)	p<0,05*
Carski rez/*Cesarean section*	39/69 (56%)	2/21 (9%)	p<0,05*
Uzrast u vreme transporta (h)/*Age at the beginning of transport (h)*	9,37	5,33	p<0,05*
Transport < 5 min.	56/69 (81%)	13/21 (62%)	p>0,05
Transport > 5 min.	13/69 (19%)	8/21 (38%)	p>0,05
Surfaktant preventivno *Prophylactic surfactant*	36/69 (56%)	14/21 (67%)	p>0,05
Surfaktant terapijski *Therapeutic surfactant*	21/69 (30%)	7/21 (33%)	p>0,05

Table 3. Characteristics of premature newborns from shorter and longer transport*s*
Tabela 3. *Karakteristike prevremeno rođene novorođenčadi iz kraćeg i dužeg transporta*

	Transport < 5 min. (n=107)	Transport > 5 min. (n=43)	p
Pol muški/*Gender male*	67/107(63%)	27/43(63%)	p>0,05
Ženski/*Female*	40/107(37%)	16/43(37%)	p>0,05
AS 5. min.	6,85	6,35	p>0,05
GS GS/*GN GW*	30,7	31,4	p>0,05
PTM (g)/*BW (g)*	1567	1734	p>0,05
Uzrast u vreme transporta (h) *Age at the beginning of transport* (h)	10,9	8,6	p>0,05
Surfaktant preventivno *Prophylactic surfactant*	64/107 (60%)	8/43 (19%)	p<0,05*
Surfaktant terapijski *Therapeutic surfactant*	31/107 (29%)	21/43 (49%)	p<0,05*
IKH (ukupno)/*ICH (total)*	70/107 (65%)	20/43 (46%)	p<0,05*
IKH I/Ii°/*ICH I/II°*	60/70 (86%)	13/20 (65%)	p<0,05*
IKH III/IV°/*ICH III/IV°*	10/70 (14%)	8/20 (40%)	p<0,05*

The regression curve gave the exact prediction of ICH grades I/II in 91.3% and of grades III/IV in 61.9% of analyzed patient sample (n=90). The confidence parameters of this procedure in order to predict grade of ICH were as follows: se=0.89; sp=0.68; ppv=0.91; npv=0.62.

Discussion

Intracrnial hemorrhage remains a significant factor of perinatal morbidity. Its exact etiology and pathogenesis is not clearly explained. Although early studies came to conclusion that subependimal hemorrhage is of venous origin, studies performed by Hambleton and Wigglesworth [9] as well as Pape and Wigglesworth [10] concluded that capillary hemorrhage is more significant than rupture of terminal veins in ICH genesis. Lately, most of the studies have shown that the majority of parenchymal hemorrhages occurs as a result of venous infarction [11] or post ischemic reperfusion [12].

Risk factors for development of ICH can be divided into following groups:

Prenatal factors – it has been doubtlessly confirmed that amniotic infection increases the risk of ICH. Studies have shown a good inverse correlation between concentrations of cytokines in blood (interleukins (IL-1β, IL-6, IL-8) and the change of hemodynamic function (systolic, diastolic and mean arterial pressure of newborn) [13]. It is believed that leukocytosis and increased ratio of immature to total neutrophil (I/T) in the first 72h of life are independent risk factors for ICH [14]. It is nor clear whether the use of tocolytics affects the development of ICH. Their aggressive use can delay labor for 48 hours to enable antenatal use of steroids [15]. Our study has not shown that the use of tocolytics has influence on the incidence of intracranial hemorrhage in general, but there was a statistically significant inverse correlation between its use and incidence of grades III/IV ICH. Antenatal use of steroids is the most important protective factor, probably as a result of direct maturing impact on fetal brain, reduction of lung disease and need for the use of inotropes [16,17]. On the other hand, this positive impact has not been proven in some studies [18]. Our study has not showed a statistically significant difference in relation to this parameter between groups of newborns with and without diagnosed ICH. However, further analysis of group with ICH has showed a statistically significant difference in relation to the antenatal steroid use and grades of ICH (ICH I/II 17/33 vs. ICH III/IV 3/18; p<0.05). It is important to mention that steroids were used antenatally in only one third of our patients (50/150), so their routine application would probably have greater impact on lowering the incidence of ICH.

Intrapartal factors – It has not been cleared yet whether the delivery mode has impact on the incidence of ICH. In one study, an increased incidence of ICH after vaginal delivery in the case of breech presentation has been determined. However, the multivariate analysis did not prove the statistical significance of this finding [19], nor did our study prove an impact of delivery mode on the incidence of ICH. In the cohort study of Thorp et al. the protective effect of Caesarean section was found only in the case of newborns under 27 weeks` gestational age [18]. This could explain the finding of our study that grades III/IV ICH developed more often in the case of vaginal delivery because the gestational age of this group was significantly lower.

Neonatal factors – Respiratory co-morbidity, and especially respiratory distress syndrome, remains a significant risk factor for the development of ICH, most probably as a result of complications of mechanical ventilation, e.g. hyper- and hypocapnia, air-leak syndromes and acidosis [19]. An early prophylactic use of surfactant in premature newborns is the cornerstone of their treatment [20]. Our study has stressed out once again the significance of the prophylactic use of surfactant in reducing not only the mortality but also the morbidity of premature newborns. Therefore it is of utmost importance to evaluate the need for endotracheal intubation and prophylactic application of surfactant in every premature newborn under 29 weeks` gestational age immediately after the initial resuscitation [21]. The neonatal transport to a tertiary perinatal centre remains a significant risk factor of ICH [22]. Our study has showed a significant difference in relation to a newborn`s age at the beginning of the transport between groups with and without ICH (7.35h vs. 12.2h;p<0.05) as well as between groups with grades I/II ICH and III/IV ICH (9.37h vs. 5.33h; p<0.05). These results lead to a conclusion that for the more favorable neurological outcome in critically ill premature newborns initial resuscitation is much more important than speed of their transport to tertiary perinatal centre [22].

As neonatal transport is considered to be an important risk factor for developing ICH, we have analyzed impact of this parameter. All performed transports have been divided into two groups according to their duration: the first group of newborns was transported from Clinic of Gynecology and Obstetrics Clinical Centre Novi Sad (transport duration 5 minutes) and the second group from regional maternity wards (Subotica, Sombor, Vrbas, Senta, Zrenjanin, Sremska Mitrovica; average transport duration 72.5 minutes). The analysis has not showed a statistical difference between these two groups in relation to gender, gestational age, birth weight, Apgar score at 5. min or age at the beginning of transport. Surfactant was given more often in the first group prophylactically (31/107 vs. 8/43; $p<0.05$) as well as therapeutically (31/107 vs. 21/43; $p<0.05$). This is probably the result of limited availability of this drug in regional maternity wards. The introduction of regular prophylactic administration of surfactant would probably lead to a better overall as well as neurological outcome of these patients. The analysis of overall ICH incidence has revealed a higher rate in the first group (70/107 vs. 20/43; $p<0.05$). However, further analysis performed in relation to a ICH grade showed a statistically significant lower incidence of grades III/IV ICH in this group (10/70 vs. 8/20; $p<0.05$). This result is in accordance with conclusion of previously published studies that incidence of grades III/IV ICH in very low birth weight premature newborns is higher if they are born in level I or II maternities and subsequently transported to a tertiary perinatal centre [23].

Conclusion

Intracranial hemorrhage remains a significant morbidity factor in premature newborns. The most important antenatal measure in order to reduce its incidence is steroid therapy. Postnatally, more favorable neurological outcome in premature newborns can be achieved rather by the prompt initial resuscitation and especially prophylactic application of surfactant than by the rapid transport of such a patient to a tertiary perinatal centre.

Literatura

1. Hohlagschwandtner M, Husslein P, Klebermass K, Weniger M, Nardi A, Langer M. Perinatal morbidity and mortality. Comparison between maternal transport, neonatal transport and inpatient antenatal transport. Arch Gynecol Obstet 2001;265:113-8.

2. Cordero L, Backes CR, Zuspan FP. Very low-birth weight infant. Influence of place of birth on survival. Am J Obstet Gynecol 1982;143:533-7.

3. Mayfield JA, Rosenblatt RA, Baldwin LM, Chu J, Logerfo JP. The relation of obstetrical volume and nursery level to perinatal mortality. Am J Public Health 1990;80:819-23.

4. Tomich PG, Anderson CL. Analysis of a maternal transport service within a perinatal region. Am J Perinatol 1990;7:13-7.

5. Burstein J, Papile L, Burstein R. Intraventricular hemorrhage and hydrocephalus in premature newborns: a prospective study with CT. Am J Roentgenol 1979;132:631-5.

6. Heuchan AM, Evans N, Henderson Smart DJ, Simpson JM. Perinatal risk factors for major intraventricular haemorrhage in the Australian and New Zealand neonatal network, 1995–97. Arch Dis Child Fetal Neonatal Ed 2002;86:F86.

7. Martin RJ, Fanaroff AA, Walsh MC, eds. Fanaroff and Martin's neonatal-perinatal medicine: diseases of the fetus and infant. 8th ed. St Louis: Mosby Elsevier; 2006. p. 879-87.

8. Volpe JJ. Neonatal neurology. 3rd ed. Philadelphia: WB Saunders; 1995.

9. Hambleton G, Wigglesworth JS. Origin of intraventricular haemorrhage in the preterm infant. Arch Dis Child 1976;51:651.

10. Pape KE, Wigglesworth JS. Haemorrhage, ischaemia and perinatal brain. Clin Dev Med 1979;69/70:133.

11. Takashima S, Mito T, Ando Y. Pathogenesis of periventricular white matter haemorrhage in preterm infants. Brain Dev 1986;8:25.

12. Volpe JJ. Intraventricular hemorrhage in the premature infant: Current concepts. Part I. Ann Neurol 1989;25:3.

13. Tauscher MK, Berg D, Brockmann M, Seidenspinner S, Speer CP, Groneck P. Association of histologic chorioamnionitis, increased levels of cord blood cytokines, and intracerebral hemorrhage in preterm neonates. Biol Neonate 2003;83:166.

14. Paul DA, Leef KH, Stefano JL. Increased leukocytes in infants with intraventricular hemorrhage. Pediatr Neurol 2000;22:194.

15. Abdel-Rahman AM, Rosenberg AA. Prevention of intraventricular haemorrhage in the premature infant. Fetal Drug Ther 1994;21:505-21.

16. Leviton A, Dammann O, Allred EN, Kuban K, Van Marter L, Paneth M, et al. Antenatal corticosteroids and cranial ultrasonographic abnormalities. Am J Obstet Gynecol 1999;181:1007-17.

17. Arad I, Baras M, Bar-Oz B, Gofin R. Neonatal transport of very low birth weight infants in Jerusalem: revisited. IMAJ 2006; 8:477-82.

18. Thorp JA. Perinatal factors associated with severe intracranial hemorrhage. Am J Obstet Gynecol 2001;185:859.

19. Shankaran S, Bauer CR, Bain R, Wright LL, Zachary J. Prenatal and perinatal risk and protective factors for neonatal intracranial hemorrhage. Arch Pediatr Adolesc Med 1996;150:491.

20. American Academy of Pediatrics, Committee on fetus and newborn. Surfactant replacement therapy for respiratory distress syndrome. Pediatrics 1999;103(3):684-5.

21. Spasojević S, Doronjski A, Kovačević B, Pavlović V, Nikolić M. Smernice za primenu preparata surfaktanta pre transporta. U: Radunović N, ur. Zbornik radova VI Kongresa perinatalne medicine Srbije i Crne Gore 18-20. maj 2007; Beograd, Srbija. Beograd: SLD; 2007. str. 198-200.

22. Spasojević S, Konstantinidis G, Doronjski A. Morbiditet i mortalitet prevremeno rođene novorođenčadi nakon započinjanja Nacionalnog programa in vitro fertilizacije – naše iskustvo. Srp Arh Celok Lek 2010;138(1-2):67-71.

23. Towers CV, Bonebrake R, Padilla G, Rumney P. The effect of transport on the rate of severe intraventricular hemorrhage in very low birth weight infants. Obstet Gynecol 2000;95:291-5.

Sažetak

Uvod
Intrakranijalna hemoragija ostaje značajan činilac morbiditeta prevremeno rođene novorođenčadi. Na njenu incidenciju značajno utiče niz činilaca, među kojima su posebno značajni odgovarajuća perinatalna zaštita kao i siguran neonatalni transport. Cilj rada bio je da se analizira incidencija i faktori rizika za razvoj intrakranijalne hemoragije kod prevremeno rođene novorođenčadi transportovane „k sebi".

Materijal i metode
Retrospektivna transverzalna klinička studija obuhvatila je 150 prevremno rođene novorođenčadi transportovane i lečene na Odeljenju intenzivne nege i terapije Službe za neonatologiju i intenzivnu terapiju Klinike za pedijatriju Instituta za zdravstvenu zaštitu dece i omladine Vojvodine u Novom Sadu u periodu od marta 2007. do oktobra 2008. godine.

Rezultati
Od 150 ispitanika, 60% (n=90/150) imalo je intrakranijalnu hemoragiju, sa statistički značajnom razlikom u odnosu na Apgar skor, gestacijsku starost, porođajnu telesnu masu, uzrast u vreme transporta i profilaktičku primenu surfaktanta. Od ispitanika sa intrakranijalnom hemoragijom, 77% (n=69/90) imalo je I/II stepen, a 23% (n=21/90) III/IV stepen intrakranijalne hemoragije, sa statistički značajnom razlikom u odnosu na gestacijsku starost, porođajnu telesnu masu, antenatalnu primenu kortikosteroida, način porođaja i uzrast u vreme transporta. Svi ispitanici transportovani su „k sebi", transportom do 5 minuta 71% (n=107/150), a dužim 29% (n=43/150). U grupi dužeg transporta uočena je statistički značajno ređa profilaktička primena surfaktanta i veća učestalost težih oblika intrakranijalne hemoragije. ***Diskusija***
Faktori rizika za razvoj intrakranijalne hemoragije kod prevremeno rođenog novorođenčeta dele se na: prenatalne (postojanje horioamnionitisa, izostanak primene tokolitika i kortikosteroida antenatalno), intrapartalne (način porođaja, perinatalna asfiksija) i neonatalne (respiratorni distres sindrom, upotreba surfaktanta, neonatalni transport).

Zaključak
Od antepartalnih činilaca za nastanak intrakranijalne hemoragije najznačajnija je primena kortikosteroida, a postpartalno profilaktička primena surfaktanta.

Ključne reči*: Intrakranijalno krvarenje; Transport pacijenta; Infant, prematurus; Faktori rizika; Perinatalna nega; Kortikosteroidi; Plućni surfaktanti + terapijska primena*

Rad je primljen 11. VIII 2009.
Prihvaćen za štampu 28. VIII 2009.
BIBLID.0025-8105:(2010):LXIII:7-8:454-458.