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AN OVERVIEW OF NEUROPROTECTIVE STRATEGIES IN PRETERM NEONATES

PREGLED NEUROPROTEKTIVNIH STRATEGIJA KOD PRETERMINSKE NOVOROĐENČADI

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Summary With advances in antenatal and neonatal therapy and care, the survival of preterm neonates, especially extremely immature, has increased. Brain injury occurs significantly more often in preterm neonates compared to full-term neonates, which is associated with a higher risk of neurodevelopmental disorders. Three common and frequent forms of preterm brain injury are intraventricular hemorrhage, white and gray matter injury. There are numerous antenatal, intrapartum and postnatal strategies in order to reduce risk of preterm brain injury and poor neurodevelopmental outcome. First of all, studies showed that antenatal corticosteroid and magnesium sulfate administration in case of threatened preterm delivery has an importance role in reducing the risk for preterm brain injury and neurodevelopmental disabilities. Also, delayed cord clamping and many interventions in early neonatal period, such as maintenance of optimal ventilation and hemodynamic stability, blood glucose monitoring concentration, recognition of neonatal seizures and administration of anti-seizure medications, use of caffeine and optimal nutrition affect the improvement of the neurological development of the preterm neonates. At the end of the 20th century, a special program for the care and assessment of the behavior of neonates, Neonatal Individualized Developmental Care and Assessment Program, was developed, which is used today in many neonatal intensive care units in order to minimize developmental delays of preterm neonates. A number of drugs and interventions whose possible neuroprotective effects are being investigated include mild hypothermia, erythropoietin, melatonin, allopurinol, stem cell therapy, maternal vitamin D supplementation during pregnancy, exosomal-based therapy, et al.

Keywords: prematurity, preterm newborn, neurodevelopmental disabilities, neuroprotection, brain injury

Sažetak Sa napretkom antenatalne i neonatalne terapije i nege, preživljavanje preterminske novorođenčadi, posebno ekstremno nezrele je poraslo. Oštećenje mozga javlja se znatno češće kod preterminske u odnosu na terminsku novorođenčad, što je povezano i sa većim rizikom od neurorazvojnih poremećaja. Tri uobičajena i česta oblika oštećenja mozga preterminske novorođenčadi su intraventrikularno krvarenje, oštećenje bele i sive moždane mase. Postoje brojne antenatalne, intrapartalne i postnatalne strategije u cilju smanjenja rizika od oštećenja mozga preterminske novorođenčadi i lošeg neurorazvojnog ishoda. Pre svega, studije su pokazale da antenatalna primena kortikosteroida i magnezijum-sulfata u slučaju pretećeg prevremenog porođaja ima važnu ulogu u smanjenju rizika od oštećenja mozga i neurorazvojnih poremećaja. Takođe, odloženo klemovanje pupčane vrpce i mnoge intervencije u ranom neonatalnom periodu, kao što su održavanje optimalne ventilacije i hemodinamske stabilnosti, praćenje koncentracije glukoze u krvi, prepoznavanje neonatalnih napada i primena lekova protiv napada, upotreba kofeina i optimalna ishrana utiču na poboljšanje neurološkog razvoja preterminske novorođenčadi. Krajem 20. veka razvijen je poseban program za negu i procenu ponašanja novorođenčadi. Neonatalna individualizovana razvojna nega i program procene, koji se danas koristi u mnogim jedinicama neonatalne intenzivne nege u cilju minimiziranja razvojnih poremećaja preterminske novorođenčadi. Brojni lekovi i intervencije čiji se mogući neuroprotektivni efekti istražuju uključuju blagu hipotermiju, eritropoetin, melatonin, alopurinol, terapiju matičnim ćelijama, suplementaciju vitaminom D kod majke tokom trudnoće, terapiju zasnovanu na egzozomima i dr.

Ključne reči: prematuritet, preterminsko novorođenče, neurorazvojni poremećaji, neuroprotekcija, oštećenje mozga

INTRODUCTION

Preterm delivery (PD) and its complications are the leading cause of death in the neonatal period, and the second cause of death for children under five years of age (1). With advances in antenatal and neonatal therapy and care, the survival of preterm neonates, especially extremely immature, has increased. The third trimester of pregnancy is a critical period of brain development. Brain growth is the most intense, neurons multiply and create numerous synapses. During this period, the fetus is in its mother's womb, tucked away and protected from all the influences of the external environment. Brain injury occurs significantly more often in preterm neonates compared to full-term neonates, which is associated with a higher risk of neurodevelopmental disorders (2-4). The most common form of preterm brain injury is intraventricular hemorrhage (IVH), bleeding from small blood vessels of the subependymal germinal matrix. Another form of brain injury in preterm neonates, called encephalopathy of prematurity, refers to multiple lesions of the white and gray matter of the brain such as activation of microglia, preoligodendrocyte dysmaturation, loss and dysfunction of oligodendrocyte, arrest of maturation of neurons and neuronal loss (3-5). The term „encephalopathy of prematurity" was first introduced by Dr Joseph Volpe in 2005 (6). There are many antenatal, perinatal and postnatal factors which are associated with preterm brain injury, such as acute and chronic hypoxia, ischemia, oxidative stress, inflammation and cytokines release, chorioamnionitis, intrauterine fetal growth restriction, mechanical ventilation (MV), pain, poor nutrition, microbiome

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dysbiosis, genetics/epigenetics factors and exposure to drugs in pregnancy (3,4,7). This article provides an up-to-date review of the literature on neuroprotective and therapeutic strategies for brain injury in preterm neonates.

CLASSIFICATION OF NEUROPROTECTIVE INTERVENTIONS FOR PRETERM BRAIN INJURY

Neuroprotection of the brain in preterm neonates and reduce the risk of neurodevelopmental disabilities is challenging. Neuroprotective interventions can be divided into three groups, antenatal, perinatal and postnatal (Table 1) (2,8,9).

Table 1. Neuroprotective interventions for brain injury in preterm neonates
Tabela 1. Neuroprotektivne intervencije oštećenja mozga kod preterminske novorođenčadi

Antenatal (Prenatal) neuroprotective interventions **Antenatalne (Prenatalne) neuroprotektivne intervencije**
▪ Antenatal corticosteroids administration Antenatalna primena kortikosteroida
▪ Magnesium Sulfate Magnezijum-sulfat
Perinatal (Intrapartum) neuroprotective interventions **Perinatalne (Intrapartalne) neuroprotektivne intervencije**
▪ Delayed Cord Clamping/Umbilical Cord Milking Odloženo klemovanje pupčanika/Ceđenje pupčane vrpce
Postnatal neuroprotective interventions **Postnatalne neuroprotektivne intervencije**
▪ Prevention of hypothermia in extremely preterm and very preterm neonates Prevencija hipotermije ekstremno i veoma preterminske novorođenčadi
▪ Glucose control Kontrola glikemije
▪ Maintenance of adequate ventilation Održavanje adekvatne ventilacije
▪ Use of methylxanthines Primena metilksantina
▪ Maintenance of hemodynamic stability Održavanje hemodinamske stabilnosti
▪ Therapy and control of neonatal seizures Terapija i kontrola neonatalnih konvulzija
▪ Optimal nutrition Optimalna ishrana
▪ Restrictive administration of blood transfusion Restriktivna primena transfuzija krvi
▪ Pain control Kontrola bola
▪ Newborn Individualized Developmental Care and Assessment Program Neonatalna individualizovana razvojna nega i program procene

ANTENATAL CORTICOSTEROID ADMINISTRATION

One of the key steps recommended in all cases of threatened PD is the administration of corticosteroids. Prenatal intramuscular administration of betamethasone or dexamethasone in the mother stimulates the fetal lung maturation, as well as enzymes that stimulate the synthesis of phospholipids and the release of surfactant in the fetal lung. In this way, the risk of developing severe forms of respiratory distress syndrome (RDS) and the need for MV is significantly reduced (5, 7, 10). At the same time, studies have shown that antenatally administered corticosteroids have an effect in preventing of cerebral white matter injury (WMI) and IVH in preterm neonates (11,12). The mechanism of action of antenatally administered corticosteroids in the prevention of IVH is the stabilization of the SGM and hemodynamic status, especially in the first 24 hours of life (9).

Antenatal administration of corticosteroids is recommended in the period of pregnancy from when the fetus acquires the ability to survive outside the uterus (23 to 25 weeks), up to 34 weeks of gestation. The optimal effect is achieved by administering the antenatal corticosteroids 24 hours to seven days before delivery. The effect of corticosteroids begins several hours after the first dose and therefore it should be administered even if it is not possible to delay the delivery for more than 24 hours (13). There are still controversial views on the use of repeated doses of corticosteroids in women at risk of PD. A repeated dose of corticosteroids reduces the risk of the need for MV, but has no effect on the mortality rate and other morbidities of the preterm neonates, reduces birth weight, as well as head circumference (14). The World Health Organization (WHO) recommends one repeated dose of corticosteroids if PD does not occur within 7 days of the first dose and there is a risk of PD within the next 7 days (13).

It is known that prenatally administered corticosteroids can have negative effects on neurological development, primarily on cognitive development and behavior, so their administration is required in accordance with current recommendations (3,13).

THE ROLE OF MAGNESIUM SULFATE IN NEUROPROTECTION

In order to improve the neurodevelopmental outcome of preterm neonates, prenatal administration of magnesium sulfate to pregnant women is also recommended. The mechanism of the neuroprotective action of magnesium sulfate is still not completely clear. The results of numerous experimental studies have shown different effects of magnesium sulfate. One of the most significant neuroprotective effects is the modulation of the N-methyl-D-aspartate (NMDA) receptor for the excitatory neurotransmitter glutamate and the reduction of excitotoxicity and NMDA receptor-mediated injury of preoligodendrocytes (3,5,9). Magnesium sulfate has an antioxidant effect and participates in the synthesis of glutathione, reduces the level of proinflammatory cytokines and the level of inflammation, and also reduces platelets aggregation (4).

Several studies have confirmed reduced incidence of cerebellar hemorrhage, reduced risk of stage 3 and 4 IVH, reduced incidence of cerebral palsy, and improved motor and cognitive outcomes (9,15,16). The WHO, Cochrane Database of Systematic Reviews and several obstetrical and pediatric societies recommend short-term use of magnesium sulfate when PD is imminent before 32 weeks of gestation (3,5,13,17).

DELAYED CORD CLAMPING AND UMBILICAL CORD MILKING

The first step in the initial care of a neonate in the delivery room is umbilical cord clamping (UCC). However, how much time should pass from birth to the moment of UCC has long been the subject of research. Several randomized controlled

trials showed that delayed cord clamping (DCC) leads to the transfusion of blood from the placenta, the volume of circulating blood of the neonate increases, which results in better hemodynamic stability. Also, DCC reduces the need for MV, decreases need for red blood cell transfusion, lower incidence of IVH by more than 50%. DCC improves cerebral oxygenation within the first 24 hours of life. According to current recommendations, if the clinical condition of the neonate allows it, DCC is necessary for at least 60 seconds after birth (3,8,9,13).

If there is a need to resuscitate the neonate immediately after birth, an alternative to DCC is umbilical cord milking (UCM), squeezing of blood from the umbilical cord from the mother to the neonate. In extremely preterm neonates, born less than 28 weeks of gestation, UCM is not considered safe due to sudden hemodynamic changes and the possible occurrence of severe IVH (13, 18). However, randomized controlled trial by Katheria A. et al. (19) compared UCM versus DCC in preterm neonates born 28 to 32 weeks of gestation and showed there was no difference in the rates of severe IVH or death.

NEONATAL VENTILATION STRATEGIES AND ITS IMPORTANCE IN NEUROPROTECTION

Maintenance of adequate ventilation is an important aspect in the postnatal care of the neonate. Considering the adverse effects of hypoxia and hyperoxia in preterm neonates, it is necessary to maintain an optimal level of oxygen saturation. As a result of numerous conditions, such as respiratory disorders, apnea of prematurity and sepsis, intermittent, transient hypoxia is common in preterm neonates. Hypoxia affects cerebral autoregulation of blood flow, which can lead to IVH. Also, in those situations, there may be cerebral WMI and dysmaturation of preoligodendrocytes (3). Kapadia V, et al. (20) showed that bradycardia (hear rate <100 beats/min more than 2 minutes) combined with low oxygen saturation (<80%) within 5 min increases the risk of mortality and IVH. Also, hyperoxia has a various of harmful effects on the brain of a preterm neonates, such as cerebral vasoconstriction and reduction of cerebral blood flow by 30-50%, impaired of angiogenesis in the periventricular zone of the immature brain, and possible ischemia and cerebral WMI. The influence of hyperoxia on neuronal damage is reported in the literature, primarily leading to pontosubicular necrosis of neurons (3).

The “European Guidelines for the Management of RDS” provide recommendations for the use of oxygen in neonatal resuscitation. The initial fraction of inspired oxygen (FiO2) for neonates born before 28 weeks of gestation should be 0.30, for neonates between 28 and 32 weeks of gestation 0.21 - 0.30, and for newborns above 32 weeks of gestation FiO2 should be 0.21. Oxygen saturation above 80% should be achieved within 5 minutes after birth. In the future, in the treatment of preterm neonates, the target oxygen saturation should be between 90 and 94% (13). However, Sotiropoulous JX, et al. (21) suggested that high initial FiO_2 (≥0.90) for resuscitation of preterm neonates born at less than 32 weeks of gestation may be associated with reduced mortality in compared to low initial FiO_2 (< 0.3).

Several observational studies have shown that hypocapnia, partial pressure of carbon dioxide (pCO2) less than 35 mmHg (4.6 kPa), and hypercapnia, pCO2 more than 60 mmHg (8.0 kPa), can cause preterm brain injury. Hypocapnia reduces cerebral blood flow and thus increases the risk for ischemic cerebral WMI. On the other hand, hypercapnia causes cerebral vasodilatation with increased cerebral blood flow that may increase the risk of intracranial hemorrhage, such as IVH. It is recommended that the target pCO2 be between 45 – 55 mmHg (6.0 – 7.3 kPa), as it has been shown to reduce the incidence of IVH and WMI (3,9).

THE NEUROPROTECTIVE EFFECTS OF METHYLXANTHINES

Caffeine, a methylxanthine drug, acts as an adenosine receptor antagonist, which are mostly found in the lung, hippocampus and neocortex. Caffeine is routinely used in neonatal intensive care unit (NICU) to treat apnea of prematurity. In addition, studies have shown that caffeine has a neuroprotective effect and improves the neurodevelopmental outcome of preterm neonates, especially motor impairment. Caffeine stimulates the maturation of oligodendrocytes and improves myelination, as well as modifies neuronal synapses (3,9,22). When administered in a higher loading dose, caffeine reduces cerebral blood flow due to vasoconstriction. Prolonged administration of caffeine reduces episodes of intermittent hypoxia in preterm neonates and thus prevents hypoxia-induced cerebral WMI (3,22).

Lodha A et al. (23) in retrospective observational cohort study showed that preterm neonates who received caffeine within 48 hours of birth had better neurodevelopmental outcome than preterm neonates who received caffein after 48 hours after birth. According to currently valid recommendations, caffeine should be administered from the first day of birth in a loading dose of 20 mg/kg intravenously, and then continued in a maintenance dose of 5-10 mg/kg/per day (5,13).

GLUCOSE MONITORING IN PRETERM NEONATES

Preterm neonates, especially those born before 34 weeks of gestation, are at high risk for developing hypoglycemia due to insufficient glycogen reserves. If it is not treated, repeated and persistent hypoglycemia can lead to neurodevelopmental disorders, since glucose is necessary for the normal development and sustainability of white matter of the brain, as well as the functioning of neurons. Hypoglycemia disrupts the energy metabolism of cells in brain tissue, primarily neurons and oligodendrocytes, which leads to brain injury in premature neonate (4,9). The European and American Associations of neonatologists and endocrinologists have defined blood glucose concentrations that require treatment (Table 2) (24).

Table 2. Blood glucose concentration and the age of the neonate for management of hypoglycemia
Tabela 2. Koncentracija glukoze u krvi i uzrast novorođenčeta za terapiju hipoglikemije

Symptomatic neonates **Simptomatska novorođenčad**
▪ < 48h: <50 mg/dL (< 2.8 mmol/L) ▪ ≥ 48h: <60 mg/dL (< 3.3 mmol/L)
Asymptomatic neonates **Asimptomatska novorođenčad**
▪ < 4h: <25 mg/dL (< 1.4 mmol/L) ▪ 4h to < 24h: <35 mg/dL (< 1.9 mmol/L) ▪ 24h to < 48h: <50 mg/dL (< 2.8 mmol/L) ▪ ≥ 48h: <60 mg/dL (< 3.3 mmol/L)

After birth, hyperglycemia is common in neonates born before 28 weeks of gestation and/or with a birth weight less than 1500 g. It is defined as a concentration of glucose in the blood higher than 7.0 mmol/L, and it occurs as a result of relative hypoinsulinism. Some studies have shown that severe and prolonged hyperglycemia is associated with the development of IVH, most likely as a result of changes in plasma osmolarity and loss of cerebral autoregulation. In order to reduce the impact of hyperglycemia on the occurrence of neurodevelopmental disorders in childhood, it is necessary to maintain the concentration of glucose in the blood between 4 and 6 mmol/L (25).

CONTROL OF NEONATAL SEIZURES AND THE ROLE OF ELECTROENCEPHALOGRAPHY

Preterm neonates are at high risk for seizures. The frequency of seizures is inversely proportional to gestational age. Recognition of seizures in preterm neonates in clinical practice can be challenging, because they can be subclinical or electrographic-only. The most common conditions and diseases in preterm neonates associated with seizures are IVH, sepsis, meningitis and transient metabolic disorders (hypoglycemia, hypocalcemia, hyponatremia). If left unrecognized and untreated, seizures can worsen pre-existing preterm brain injury. Also, neonatal seizures increase the risk for later onset of epilepsy and neurodevelopmental disorders during childhood. The "gold standard“ for detection neonatal seizures is video-electroncephalography (EEG), but it is not available in all neonatal centers and its interpretation requires special education. Amplitude-integrated EEG (aEEG) is more commonly used in the NICU to detect electrographic seizures. When seizures are detected, antiseizure medication should be started, because early treatment with antiseizure medication reduces the risk of more serious preterm brain injury and better neurodevelopmental outcome (4,9,26,27).

MAINTENANCE OF HEMODYNAMIC STABILITIY

After PD physiological transition from fetal to neonatal circulation is affected by several factors, such as immaturity of organs and organ systems, pathological maternal conditions and resuscitation after birth. Also, delayed closure of the ductus arteriosus after birth contributes to their hemodynamic instability. In preterm neonates, circulatory insufficiency and hemodynamic instability are most often clinically manifested by hypotension (28). Maintenance of optimal cerebral blood flow by the mechanism of cerebrovascular autoregulation requires maintenance of blood pressure (BP) values in the "normal" range. Recognizing hypotension in a preterm neonates is very important because of the danger of cerebral hypoperfusion and consequent WMI (4). However, systemic hypotension during first 24 hours of life associated with stage 3 and 4 IVH. Hypotension in the early neonatal period in preterm neonates is an independent predictive factor of poor neurodevelopmental outcome (29,30).

On the other hand, hypertension is not common in NICU. It’s found in less than 3% of neonates. An increase in BP, especially suddenly, can lead to the rupture of vulnerable blood vessels in the area of the SGM and the appearance of IVH. Also, there may be rupture of vulnerable small blood vessles in the periventricular zone of the brain and the formation of massive hemorrhagic lesions in the white matter of the brain (4,31).

Given that a decrease or increase in BP above the reference range for gestational age can lead to ischemic and hemorrhagic lesions in the brain of a preterm neonates, hemodynamic monitoring is important. First of all, a daily clinical and laboratory assessment of the hemodynamic stability of neonates in the NICU is required. The most common clinical parameters for monitoring neonatal hemodynamics are heart rate, BP and urine output, while the laboratory analyzes monitor arterial pH, serum lactate, urea and creatinine concentrations. Also, functional echocardiography has great importance for the hemodynamic assessment of neonates in the NICU, but also for monitoring the effects of the therapy applied in order to maintain hemodynamic stability. Near-infrared spectroscopy (NIRS) can be used to assess blood flow and perfusion in the target organ. However, the role of NIRS in hemodynamic monitoring in NICU in preterm neonates is still under investigation (29).

NEWBORN INDIVIDUALIZED DEVELOPMENTAL CARE AND ASSESSMENT PROGRAM

After birth, the preterm neonate is removed from protected environment in mother’s womb and in order to survive it often needs treatment in NICU, where it is connected to numerous devices and monitors, exposed to sounds and light, undergoes numerous repeated diagnostic and therapeutic procedures and their sleep is interrupted. In these circumstances, the immature nervous system, which is in a very sensitive stage of development, is overwhelmed by numerous sensory stimuli, which it cannot overcome may result in poor neurodevelopmental outcome (3,32).

Neonatal Individualized Developmental Care and Assessment Program (NIDCAP) is a specific method of care and assessment of neonate behavior. Also, NIDCAP is an early neuroprotective intervention program, individually adapted to each neonate and family-centered. The program was created in the USA in 1986, and based upon the Synaptic Theory of Development. The NIDCAP program includes adequate positioning (flexed position of the body and midline head position), minimal and careful handling, reduce sensory stimuli and family involvement in the treatment and care of the neonate (3,32).

Kangaroo Mother Care (KMC), a form of skin-to-skin contact between mother or father and neonate, plays an important role in the care of preterm neonates. Studies have shown numerous advantages of this method in the care of a preterm neonates, among other things, a favorable effect on the neurodevelopmental outcome, especially cognitive functions (3).

FUTURE POTENTIAL NEUROPROTECTIVE STRATEGIES

A number of preclinical and clinical studies are underway investigating the neuroprotective effect of drugs and interventions. Results in preclinical studies suggest that mild hypothermia of the head or whole body of neonates born between 33 and 35 weeks of gestation applied during the first 6 hours of life reduces brain injury (2,7). Erythropoietin plays an important role in erythropoiesis and is used in the prevention and treatment of anemia of prematurity. In addition, erythropoietin and

its receptor participate in nervous system development. In preclinical studies, the role of erythropoietin in the repair of brain tissue injury and its role in brain development has been confirmed. Also, evidence in clinical studies suggests a neuroprotective effect of erythropoietin (2,5). Other drugs, supplements, and interventions whose possible neuroprotective effects are being investigated include melatonin, allopurinol, stem cell therapy, maternal vitamin D supplementation during pregnancy, exosomal-based therapy, et al. (2,3,5,7).

CONCLUSION

Prematurity is associated with a high risk of poor neurodevelopmental outcome. Therefore, prevention of PD is very important. There are many interventions and drugs that can be administered prenatally and postnatally in order to prevent preterm brain injury and neurodevelopmental disabilities. Also, a number of promising studies are underway investigating the neuroprotective effects of many pharmacological agents and interventions that are believed to contribute to the reduction of preterm brain injury and neurodevelopmental disorders during childhood.

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