THE ROLE OF ERYTHROPOIETIN IN THE PRETERM INFANTS TREATMENT

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S u m m a r y. Anemia in premature infants is a major problem in modern neonatology. Due to the lower prenatal body's iron stores, increased congenital and perinatal infection-rate and erythrocytes hemolysis, premature infants are more prone to developing anemia. Another factor contributing to anemia is the lack of endogenous erythropoietin (EPO). The implementation of recombinant human erythropoietin in the 90XX century as a therapy revolutionized the treatment of anemia in these patients. Recent reports describe a wider range of application of this hormone in neonataly. Furthermore, studies also show the significant neuroprotective role of erythropoietin. With the increasing rate of the premature births the erythropoietin therapy is becoming common practice.

K e y w o r d s: recombinant human erythropoietin, anemia of preterm infants.

CASE REPORT

The female newborn from the first pregnancy, delivered by C- section by 34 weeks. The infant was born with the birth weight of 1100g, the length of 41cm, rated at 8-9 Apgar-points. The pregnancy was complicated by maternal hypertension, with preeclampsia before delivery. The initiating breaths Neopuff were applied after birth, afterwards the proper breathing was regular and efficient. The newborn was sent to the intensive care unit and the vital signs were monitored - parameters were normal, cardiopulmonary efficient. Because of hypoglycemia (blood glucose level -30mg/dl) the infant received a bolus of 10% glucose, followed by an infusion of parenteral nutrition. The control blood glucose levels were normal. The central venous catheter was founded by the umbilical vein, and bacteriological and laboratorial tests were collected. (Blood morphology on first day WBC - 5,26 x10 ^ 3/ml, RBC - 4, 73 x 10 ^ 6/ml; Hgb - 16, 9 g/dl, Hct - 51, 5%, MCV - 108, 8FL, MCH - 35, 7PG, MCHC - 32, 8 g/dl, PLT - 257 x 10 ^ 3/ml). The anterior-posterior chest radiograph showed a paracavital inflammation in the right lung. The laboratorial tests showed a tendency to leukopenia, the haemoculture was negative. An Empirical antibiotic treatment (Ampicicillin-150mg/kg/day, Gentamicin-4mg/kg/36h) was used over the next 7 days. From the 4th day of life, the newborn tolerated the enteral maternal nutrition, which was started with a low dose and the amount was gradually increased, and it was supplemented with the parenteral nutrition infusions till the 9th day of life. The control blood test on the 7th day of life: WBC -8, 55 x 10 ^ 3/ml, RBC - 4, 94 x 10 ^ 6/ml, Hgb - 17, 5 g/dL, HCT - 51, 5%, MCV - 104.3 fl, MCH - 35, 4 pg, MCHC - 34 g/dL, PLT - 231 x 10 ^ 3/ul. Human fortifier milk, iron preparation (Actiferol at a dose of 6 mg/kg/day) and hematopoietic vitamin (Ac.folici a 5mg: 1 x 1/2 tablet, Vit.B6: 1 x 1/2 tablets) were included from the 13th day of life to provide the steady body weight increase.

In the view of the gradual anemia (blood morphology on 30th day of life: WBC - 6,72 x 10 ^ 3/ul; RBC-3, 64 x 10 ^ 3/ul Hgb - 11, 9 g/dL, HCT - 34, 4%, MCV - 94, 4FL, MCH - 32, 6 pg, MCHC - 34, 6 g/dl, PLT - 494 x 10 ^ 3/ul; blood morphology on 36th day of life WBC - 7, 24 x 10 ^ 3/ul, RBC - 2,92 x 10 ^ 5/ul; Hgb - 9,2 g/dL, HCT - 26,6%, MCV

- 91, 1fl, MCH - 31, 5PG, MCHC - 34, 6g/dl, PLT - 667 x 10 ^ 3/ul) the treatment with erythropoietin was started-500J subcutaneously, given in a single dose - to continue on an ambulatory basis. The patient was discharged home in the stable condition: 36 days old with the body weight of 1785g. Iron supplementation (8-10mg/kg) and haematopoietic vitamins were recommended.

The child was taken into care in the Neonatal Pathology Clinic. The course of treatment with erythropoietin was continued- a dose of 500J was injected subcutaneously three times a week, including the permanent iron supplementation (8-10mg/kg/d). After nine doses of medication, the parameters of red blood cells system were normalized. The control blood count after 2 months of treatment: WBC - 9,75 x 10 ^ 3/ul, RBC - 4,27 x 10 ^ 6/ul; HGB - 12,3 g/dL, HCT - 35,2%, MCV - 82, 4FL, MCH - 28,8 pg, PLT - 517 x 10 ^ 3/ul. Currently, the treatment is continued as the prophylactic dosage of iron preparations 2 mg/kg/day.

The treatment with erythropoietin helped to avoid the additional transfusion burdened with a greater risk of adverse events compared with medical therapy.

DISCUSSION

Anemia is a hematological problem related to prematurity. The most responsible for the inadequate resources of iron accumulated in utero are: shorter survival time of red blood cells, lower levels of endogenous erythropoietin and frequent iatrogenic blood loss.

The iron transfer from the mother to the fetus begins in early pregnancy-in the first trimester, but the significant amount of Fe is accumulated from the 32nd week of pregnancy. [7].

In the full-term infant, the amount of accumulated Fe in the organism is about 75mg/kg of body mass. The transplacental iron transport is unidirectional-only in "mother to child". It is not dependent on the level of iron in the mother – it occurs also in the iron deficiency during pregnancy. The increased number of transferrin receptors in the placenta contributes to an active, competing against the pregnant women transport of iron to the fetus. Approximately 70% of the iron contained in the child's hemoglobin up to 1st year of life comes from the prenatal period, it is the mother's iron. In the second year of life, this percentage decreases to 40% [2, 6].

The reduced red blood cell survival time in the newborn – especially in the premature infant- has a significant impact on the deterioration of haematological parameters [1].

The endogenous erythropoietin deficiency plays also an important role in the pathogenesis of anemia in prematurity. Human erythropoietin is a glycopeptide produced in response to hypoxia in renal parenchymal cells and hepatocytes of the fetal stage. There is a circadian rhythm with a maximum of erythropoietin secretion at night. Erythropoietin does not cross the placenta. Serum EPO concentrations in preterm infants is less than 10U/ml and it reaches 15-30U/ml in older children and adults [1]. The concentration in preterm reflects only the fetal production [8].

EPO regulates the number of red blood cells via a direct effect on erythropoiesis maintaining adequate oxygenation of tissues . In the bone marrow, EPO binds to its receptors located on the precursors of red blood cells by inhibiting their apoptosis and stimulates their maturation. EPO concentration increases to the response of hypoxia in the blood reaching renal and hepatic tissues. The hypoxic stress causes its significant ejection. EPO stimulates the production of young blood platelets and activates endothelial cells- they connect the blood platelets to their surface to seal the vessel [3].

Many clinical studies demonstrated the protective effect of EPO on brain cells and spinal cord during the hypoxia . EPO and its receptors are detectable in the brain during the early weeks of fetal life. The neuroprotective role of EPO is attributed to its inhibitory effect on apoptosis by inducing the antiapoptotic factors, decreasing the sensivity to the toxic effects of glutathione produced during hypoxia and the antioxidant effect by using the free iron ions in the process of erythropoiesis [5].

Before the era of treatment with erythropoietin, the essential method to prevent the significant anemia was the blood products transfusion [1].

The primary goal of the erythropoietin treatment is to avoid complementary transfusions, which involves a lot of undesirable consequences. Blood transfusion is associated with the risk of transmission of viral infections, metabolic complications in the form of hyperglycemia, hyperkalemia, metabolic acidosis, circulatory overload, hyperferremia, and graft versus host disease (GVHD) [4].

Not without significance is the fact that there are some possible complications of early transfusion in the form of bleeding into the central

nervous system and an increased risk of necrotising enterocolitis after late transfusions, especially in preterm infants about 3 weeks of life. There is also the risk of prematurity retinopathy (ROP) especially when larger volumes of kkcz transfusions are derived from adults (cells with nearly 100% of the content of HbA with 2,3-diphosphoglicerate exhibiting affinity only to the beta chains) [8].

The use of EPO is common in neonatal wards, the use in the ambulatory care for the prematurely born infant is also more and more common.

The recombinant human erythropoietin treatment is usually carried out by subcutaneous injections available in pre-filled syringes.

The therapy usually starts with the dosage of 250 j.m/kg body weight three times a week.

The therapy is continued for at least 4-6 weeks. The concomitant treatment with the increased doses of iron preparations to 6-8mg/kg/day is necessary.

In the clinical practice, two methods of the erythropoietin treatment are used- early and late supply. The early administration of EPO is considered to 8th day of life and it is mostly supplied to the babies born prematurely with very low and extremely low birth weight-usually about the 3rd day of life. The late supply of EPO is used in a situation where the parameters of red blood cells decrease. Currently there is an insufficient evidence for the superiority of any of the two ways of supply to avoid additional transfusions. In the light of recent reports, there may be a risk of the increased risk of the prematurity retinopathy (ROP) associated with the early supply of EPO. This adverse effect of EPO in preterm infants may be due to its angiogenic activity - in this case, on the retinal vessels [1].

Numerous studies confirm the efficacy of EPO treatment. It is has been used in neonatology and pediatrics from the 1990s. As other forms of treatment it is associated with the probability of side effects. The doses used in neonatology seem to be free of the majority of adverse effects identified especially in adults with renal insufficiency (hypertension, bone pain, rash, thromboembolic complications, acquired selective red cell aplasia). Only transient neutropenia was registered in children [1]. Thus, on the basis of the previous studies, the treatment with EPO seems to be as safe as possible in the pediatric population.

If patients do not respond to EPO therapy with increase hemoglobin levels, the presence of other causes of anemia should be considered-such as occult blood loss, haemolysis. The most common causes of the inadequate response to treatment is iron deficiency, or too small dose of iron used during EPO therapy, infection, improper dosage, vitamin B6 deficiency, folic acid, and hypoproteinemia. In light of current reports, anemia causes the slower pace of physical and intellectual development, and has a negative impact on the development of the central nervous system (CNS) in children. In the neonatal population of premature babies, it seems to have a great importance.

CONCLUSIONS

1. Actual knowledge allows the safe use of EPO with indisputable benefits in the prophylaxis and treatment of anemia of prematurity.
2. The primary goal of the erythropoietin treatment is to avoid complementary transfusions, which involve a lot of undesirable consequences.
3. The subcutaneous erythropoietin treatment - irrespective of the treatment regimen- requires the increased doses of iron preparations to 8-10mg/kg/day.

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