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Anemia of Prematurity – Erythropoietin Prophylaxis and Factors that Influence It

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Abstract.

Purpose: To examine the prophylactic usage of recombinant human erythropoietin beta (EPO) for the anemia of prematurity and the influence of early blood transfusions (BTs), infections and multiple births on it.

Patients and methods: 135 newborns, born before 29th gestational week (GW), were divided into: control group 0 without and case group 1 with EPO-prophylaxis. The group 1 was separated into: according to the presence of early BTs (before postnatal 28th day) – with and without them; according to the presence of infection – with intraamniotic, with nosocomial and without infections; singletons and twins. The effect of EPO-prophylaxis was evaluated by the frequency of late BTs (after 28th day).

Results: The frequency of late BTs (per one patient) was as follows: in group 0 – 1,5±1,3, and in group 1 – 1,0±1,1 (p 0,02); in the subgroups with early BTs – 1,1±1,1, and in without them – 0,5±0,7 (p 0,015); in the subgroups with intraamniotic infections 0,9±0,9, with nosocomial infections – 1,6±1,3, and without infections – 0,6±0,7 (p 0,0000); in the subgroup of singletons – 1,0±1,1, and of twins – 1,0±1,0 (p > 0,05).

Conclusions: EPO-prophylaxis was effective in the infants, born before 29th GW, but early BTs and nosocomial infections compromised it, and multiple births did not influence it.

Keywords: anemia of prematurity, erythropoietin, blood transfusion, neonatal infection.

INTRODUCTION

According to the pathogenesis, the anemic conditions in the neonatal period are classified as [1]: hemolytic (ABO- and Rh-incompatibilities, congenital spherocytosis, G-6-PD-deficiency), hypoplastic (Parvovirus B19, Diamond-Blackfan anemia, α-thalassemia, sideroblastic anemia, *anemia of prematurity*), post hemorrhagic (after various blood losses) and anemia in critical illness.

The blood transfusions (BTs) in newborns are early (before 28th postnatal day) and late (after that) which is based on their different causes. The early anemia are due to the blood losses and/or hemolysis mostly, and the late anemia – to the fast expansion of blood volume as result of accelerated growth, nutritive deficiencies and depression of erythropoietin synthesis which are the main determinants of the diagnosis 'anemia of prematurity' (AP). Other mechanisms (infection, immune dysfunction, metabolic disturbances) compromise additionally the erythropoiesis of the ill babies.

Modern therapeutic approach to minimize BTs in the NICU includes: limitation of the phlebotomy blood losses, strict blood transfusion criteria and therapeutic or prophylactic usage of recombinant human erythropoietin (rHuEPO) with parallel iron and vitamin supplementation. The infants with very low (VLBWI) and extremely low birth weight (ELBWI) continue to require a lot of BTs during their hospital period despite of the clinical practice evolution.

PURPOSE: To investigate the effect of prophylactic usage of rHuEPO-ß in preterm infants and the influence of early BTs, infection and multiple births on it.

MATERIAL AND METHODS:

The study is prospective and obtains period from 2004 to 2012. It is in accordance with the ethical standards (confirmed by the Ethical Committee of the Medical University of Pleven, Bulgaria).

PATIENTS: 135 newborn babies who were treated in the Neonatal Department, University Hospital of Pleven, Bulgaria.

Including criteria:

- Born before 29th gestational week (GW) – the gestational age (GA) was calculated by the mother amenorrhea and by the New Ballard score;
- Survived after the early neonatal period;
- Without surgical complications;
- Good nutritive tolerance to the end of the 2nd postnatal week (oral intake of 100 ml/kg/day milk/formula);
- Monitored to the discharge (or to the term).

The patients were divided in *two main groups* – control and case, and *subgroups* of the case group (Table 1).

STUDY DESIGN:

The *iron* and *vitamins substitution* was administered in all patients:

- Iron (as Ferric proteinsuccinylate) 4 mg/kg actual weight/day p.o.;
- Folic acid 0,04 mg/day p.o.;
- Vit. B_{12} 50 mcg i.m. once a week.

EPO-prophylaxis schedule: 250 E/kg birth weight/per week, divided in 3 doses; i.v. or s.c.; continues to the 35th postconceptual week.

The effect of the EPO-prophylaxis was estimated by the incidence of the late BTs.

The BTs were administered according to the accepted in our department *transfusion protocol.*

STATISTICAL ANALYSIS:

The data were calculated using software statistical packages STATGRAPHICS v. 4.0; SPSS v. 13.0 and EXCEL for Windows. The results were described by tables, graphics and numeric values. The parametric and non-parametric tests were applied for analyzing and comparison of the results and hypothesis verification. Different kinds of regression models were applied to determine relationships between the variables. The significance of the conclusions was fixed by $p < 0,05$.

RESULTS:

The groups were comparable by the characteristic indices (Table 2). The EPO-prophylaxis reduced significantly late BTs, i.e. was effective.

According to the beginning of the EPO-prophylaxis, 3 groups were compared: without (group 0), with early (group 1.1) and with late (group 1.2) prophylaxis. It was proven that EPO-prophylaxis will be effective if it is administered after 8th postnatal day (Fig 1; *there was a significant difference between groups 0-1.2).

According to the presence of early BTs, the EPO-prophylacted infants were divided in 2 subgroups: A1 – with, and A0 – without early BTs which were compared to EPO-non-prophylacted group 0. It is clearly visible that early BTs compromise the effect of EPO-prophylactic (Fig 2; *there was a significant difference between groups 0-A0).

The control group 0 was compared with the next subgroups: B0 – without, B1 – with congenital, and B2 – with nosocomial infection. The frequency of late BTs was following: group 0 – 1,6±1,3; B0 – 0,5±0,6; B1 – 0,5±0,5; B2 – 1,4±1,1. The subgroup B2 was in most unfavorable condition – the frequency of late BTs was the same as in non-prophylacted group 0 (Fig 3; *there was not a significant difference only between groups 0-B2 and B0-B1). The congenital infections did not have any impact on the bone morrow activity – the effect of EPO-prophylactic was comparable with those in the non-infected infants.

The impact of the multiple births on the effectiveness of EPO-prophylactic was assessed too. The non-prophylactic group 0 was compared with the EPO-prophylacted singletons (subgroup C1) and with the EPO-prophylacted twins (C2). The late BTs frequency in group 0 was 1,5±1,3; in group C1 – 1,0±1,1; and in group C2– 1,0±1,0. The p-value is 0,08 but only one of the post-hoc tests determined statistical significant difference between groups 0 and C1. Therefore the EPO-effectiveness was found to be equal in both singleton and twin groups (Fig 4; *there was not a significant difference between groups).

DISCUSSION:

The hemopoiesis starts in the blood islands of the yolk sack [2, 3]. The liver becomes the main hemopoietic organ in the 5^{th}-6^{th} GW immediately after the beginning of blood circulation. The bone morrow becomes the main erythropoietic organ after the 6^{th} m.l. [2, 4]

Growth factors control the proliferation, differentiation and surveillance of the hemopoietic stem cells and corresponding progenitor cell lines. The erythtopoietin (EPO) is a primary specific growth factor regulating erythropoiesis. It is released due to hypoxia and the bone morrow is its target organ. The primary source is the liver Kupffer cells of the fetus. This function is exercised postnatal by the peritubular renal cells [2]. The shift from liver to kidney EPO-production starts in the last GW and continues to the 4^{th}-6^{th} postnatal week [3]. EPO cannot cross the placenta so that its fetal levels reflect its own synthesis.

The hemoglobin decreases in the first months of life both in the mature and premature infants, i.e. this is the *physiological anemia of the infancy* [5]. The arterial oxygenation raises sharply after the birth that results in decreased EPO-synthesis and Rbc-production respectively. The drop of Hgb in the premature infants as result of postnatal erythropoiesis suppression is more marked and more prolonged. This anemia is defined as *anemia of prematurity* (AP) and it is normocytic, normochromic and with low EPO-levels [6, 7, 8]. AP occurs often in the infants, born before 32^{nd} GW and its incidence is inversely proportional to the GA and the birth weight. The peak of Hgb-drop is around 3^{rd}-12^{th} postnatal weeks and may persist to 3-6 months.

AP is due to diminished production, shortened life and increased losses of Rbc.

The inadequate Rbc-production is due to the low EPO-levels and to the nutritive deficiencies (iron, vitamins – B_{12}, folic acid, E). Low EPO-levels are primary physiological condition in the infants, born before 32^{nd} GW, and secondary pathological condition in the ill mature and premature newborns.

The kidney produces EPO due to hypoxia faster than liver. So the liver may produce only 10% of EPO which the kidney will produce in the same circumstances. Therefore the hypoxia has to be more prolonged than needed for kidney to stimulate the liver EPO-production which predominates in the premature infants [2]. So the Rbc-production of the ELBWI is diminished even in marked anemia.

The human recombinant erythropoietin (rHuEPO) was cloned at first in 1985. The first publication of EPO-application in the premature anemic newborns was published in 1990. A lot of similar messages proving different levels of therapeutic success came into view after that [9, 10, 11].

Many studies found out that the premature infants may answer to the exogenous rHuEPO by a vigorous reticulocytosis. The number of the late BTs decreases [12]. The studies proved that the most immature infants are capable to response to such treatment and the drug is safe for them [13, 14].

Our investigation demonstrates significant reduction of the late BTs in the newborns, born before 29th GW.

Beginning of EPO-prophylaxis is relevant to the bone morrow readiness to response and to the EPO-using in other biological needs, as well as to its interacting with other growth factors. There are a few publications for the effectiveness of early and late EPO-prophylaxis [15, 16]. Our study proved *significant reduction of the late BTs by the late EPO-prophylaxis,* i.e. it is effectively. The early EPO-administering may be useful because of the other endogenous effects in the extremely immature newborns [17].

BTs are another factor which influences natural erythropoiesis by the depression of the EPO-secretion. The last one is a result of the difference between neonatal and adult Hgb – the transfusion of great amount of HgbA displaces the O_2-dissotiation curve on the left, the O_2-saturation increases and the stimulating role of the hypoxia on the EPO-production decreases [18, 19, 20].

The EPO-depression is obviously a main factor which *compromises the EPO-prophylactic effectiveness after early BTs.* This consequence was proven in our

patients. Probably, the EPO-doses have to optimize to achieve better effect (our protocol is based on the minimal recommended prophylactic doses).

EPO has immunomodulating and anti-inflammatory effects. Therefore the endogenous EPO depletes quickly in the presence of the infections in the background of the compromised immunity (prematurity). This aggravates by the infection generated hemolysis, iatrogenic (medications) and toxic induced bone morrow suppression, predominantly concerning of the white cell line, as well as by the diminished bio accessibility of the rapid iron depletion (by the microorganism and by the immune reactions) [21, 22].

The congenital and nosocomial infections have different etiopathogenesis, therefore the subgroups in our study are defined by the infection type. The different importance of the congenital and nosocomial infections was proven. *The nosocomial infection* influenced significantly the erythropoiesis and *the EPO-prophylaxis was not effective.* The reason of this phenomenon may be found in the etiological agent nature and in the background allowing the development of this complication.

The twins are the interesting case. The investigations are directed to the congenital anomalies and complications due to IVF because of the higher frequency of the multiple pregnancies after IVF compare to biological conception. There are not enough investigations about comparison of the AP-course in the premature singletons and twins. The intrauterine competition for nutritive components is supposed. *The EPO-prophylactic effectiveness is the same in the both groups* according to our data.

CONCLUSIONS:

According to our study, the EPO-prophylaxis reduced significantly the number of late BTs in the babies, born before 29th GW. The effectiveness of this prophylaxis will be optimize if EPO is administered after 8th postnatal day, if there are not early BTs or superimposed nosocomial infection. The multiple births had not any relation to the EPO-prophylaxis effectiveness in our patients.

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