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Evaluation and Treatment of Anemia in Premature Infants

Edo Hasanbegovic¹, Nermina Cengic¹, Snijezana Hasanbegovic¹, Jasmina Heljic¹, Ismail Lutolli¹, Edin Begic²

¹Pediatric Clinic, University Clinical Center Sarajevo, Sarajevo, Bosnia and Herzegovina

²Faculty of Medicine, Sarajevo School of Science and Technology, Sarajevo, Bosnia and Herzegovina

Corresponding author: Edo Hasanbegovic, MD, PhD, Pediatric Clinic, University Clinical Center Sarajevo, Sarajevo, Bosnia and Herzegovina. mail: hasanbegovic.edo@gmail.com.

ABSTRACT

Introduction: Anemia in preterm infants is the pathophysiological process with greater and more rapid decline in hemoglobin compared to the physiological anemia in infants. There is a need for transfusions and administration of human recombinant erythropoietin. **Aim:** To determine the frequency of anemia in premature infants at the Pediatric Clinic, University Clinical Center Sarajevo, as well as parameter values in the blood count of premature infants and to explore a relationship between blood transfusions with the advent of intraventricular hemorrhage (determine treatment outcome in preterm infants). **Patients and methods:** Research is retrospective study and it included the period of six months in year 2014. Research included 100 patients, gestational age < 37 weeks (premature infants). Data were collected by examining the medical records of patients at the Pediatric Clinic, UCCS. **Results:** The first group of patients were premature infants of gestational age ≤ 32 weeks (62/100) and the second group were premature infants of gestational age 33-37 weeks (38/100). Among the patients, 5% were boys and 46% girls. There was significant difference in birth weight and APGAR score among the groups. In the first group, there were 27.42% of deaths, while in the second group, there were only 10.53% of deaths. There was a significant difference in the length of treatment. There was a statistically significant difference in the need for transfusion among the groups. 18 patients in the first group required a transfusion, while in the second group only 3 patients. **Conclusions:** Preterm infants of gestational age ≤ 32 weeks are likely candidates for blood transfusion during treatment. Preterm infants of gestational age ≤ 32 weeks have the risk of intracranial bleeding associated with the application of blood transfusion in the first week of life.

Keywords: Anemia, preterm infants, blood transfusion.

1. INTRODUCTION

The World Health Organization (WHO) has defined *preterm birth* as delivery before 37 completed weeks of gestation (gestational age is reported in terms of completed weeks (i.e., one never rounds gestational age up, so 36 weeks and 6 days of gestation is 36 weeks and not 37 weeks of gestation)) (1). All newborns are subject to decline in hemoglobin levels in the first weeks after birth. In neonatology, this condition is often called physiological anemia of the newborn. In healthy term infants, clinical signs or symptoms of anemia are absent; this normal decline in Hb is referred to as “physiologic” or “early anemia of infancy” (2). It was noted that the lowest value of hemoglobin in term infants rarely fall below 100 g/L in age from 10 to 12 weeks

(3). In contrast, anemia in preterm infants (anemia of prematurity) is the pathophysiological process with larger and faster drop in hemoglobin. Consequently, there is a need for blood transfusion and application of human recombinant erythropoietin. Generally, it is considered that at the age of 4-6 weeks, premature infants of birth weight between 1000 and 1500 grams have hemoglobin value about 80 g/L, while premature infants of birth weight less than 1000 grams have hemoglobin value about 70 g/L (3). Preterm infants are faced with the appearance of anemia of prematurity due to several main reasons (4). The first is the shortened gestational age - when it is shorter the clinical presentation is more severe. Another reason is the underdevelopment of the hematopoietic

system in preterm infants (2). The third, very important cause of anemia are repeated acts of taking blood for laboratory analysis.

2. AIM

The aim of this study was to determine the frequency of clinical manifestations of anemia in premature infants at the Pediatric Clinic, University Clinical Center Sarajevo, accompanied by a drastic drop in hemoglobin and hematocrit in the blood count and a need for treatment in high-risk groups of premature infants of gestational age below 32 weeks, compared to a group of premature infants over 32 weeks and the linkage of perinatal and neonatal risk factors with the development of anemia of prematurity as well.

3. PATIENTS AND METHODS

Research has been set as a retrospective analysis of the characteristics of anemia of prematurity in the period of the first six months of year 2014. The study included 100 patients, gestational age < 37 weeks (premature infants), who were admitted to, after giving birth, at the Department of Neonatal Intensive Care at the Pediatric Clinic, of Clinical Center of Sarajevo University (UCCS). Inclusion criteria in the study were: the patient is a premature infant gestational age < 37 weeks and the patient's first admission at the Department of Neonatal Intensive Care. Exclusion criteria were no data on: gestational age of the patient, the blood count at the admission, the number of received transfusions and administration of iron therapy. Analytical and descriptive methods were used. Data were collected by examining the medical records of patients at the Pediatric Clinic, UCCS. Statistical analysis of the collected data was performed through SPSS ver. 21.0. Data obtained after statistical analysis were presented in tables and figures, using Microsoft Office Excel 2007. Statistical analysis was performed by it-test. The level of significance of $P < 0.05$ was considered statistically significant.

4. RESULTS

There were two groups of patients, the first, children of gestational age ≤ 32 weeks, and the second, children of gestational age 33–37 weeks. In the first group there were 62/100 patients (62 %), while in the second 38/100 (38 %) patients. The larger number of patients in each group were males (Table 1). Data analysis demonstrated a statistically significant difference ($P < 0.01$) between the two groups of patients, in terms of body weight at birth (Table 2).

GD (weeks)	Male	%	Female	%	Total	%
≤ 32	34	54.84	28	45.16	62	100
33-37	20	52.63	18	47.37	38	100

Table 1. The gender structure of patients by the groups

GD (weeks)	Average	SD	Min	Max	P-value
≤ 32	1349	516	500	2300	<0.01
33-37	2242	461	1350	3150	

Table 2. The birth weight of patients

There was a statistically significant difference between the infants of gestational age ≤ 32 weeks and gestational age 33–37 weeks, in terms of APGAR score in the first minute ($P < 0.001$), and after 5 minutes ($P < 0.004$) (Table 3).

GD (weeks)	Average	SD	Min	Max	P-value
≤ 32	6 / 7	2 / 2	1 / 2	10 / 9	<0.001 / <0.004
33-37	7 / 8	2 / 1	3 / 5	10 / 10	

Table 3. APGAR score in the first and fifth minute

In the first group, 16.13 % of children were reanimated, and in the second 5.26 %. The statistical analysis did not show any significant difference in the number of resuscitations of children between groups. In terms of deaths, 27.42 % of children in the first group had a lethal outcome, and 10.53 % of children in the other. It is proved a statistically significant difference in mortality between groups ($P < 0.04$).

GD (weeks)	Resuscitation	%	Deaths	%
≤ 32	10	16,13	17	27.42
33-37	2	5,26	4	10.53
P-value	<0,105		<0,04	

Table 4. The number of resuscitation and deaths

Statistical analysis demonstrated a statistically significant difference in the number of erythrocytes between groups of patients gestational age ≤ 32 weeks, and those of gestational age 33–37 weeks (Table 5.). However, there wasn't a significant difference in the level of hemoglobin and hematocrit between the two groups (Table 6-7).

GD (weeks)	Average	SD	Min	Max	P- value
≤ 32	4.39×10^{12}	0.62	2.6×10^{12}	5.6×10^{12}	<0.003
33-37	4.52×10^{12}	0.71	3.27×10^{12}	6.23×10^{12}	

Table 5. The number of erythrocytes in blood count at admission

GD (weeks)	Average	SD	Min	Max	P- value
≤ 32	155 g/L	22	92 g/L	199 g/L	<0.062
33-37	167 g/L	28	113 g/L	230 g/L	

Table 6. The value of hemoglobin in blood count at admission

GD (weeks)	Average	SD	Min	Max	P- value
≤ 32	0.49 L/L	0.07	0.32 L/L	0.61 L/L	<0.318
33-37	0.51 L/L	0.08	0.34 L/L	0.68 L/L	

Table 7. The value of hematocrit in blood count at admission

Out of 62 children, 18 children gestational age ≤ 32 weeks received a blood transfusion, while only 3/38 of children gestational age 33–37 weeks needed transfusion (Table 8). Statistical analysis showed a significant difference ($P < 0.01$) between mentioned groups in terms of the need for transfusion.

GD (weeks)	Number of infants	%	P- value
≤ 32	18	29.03	<0.01
33-37	3	7.9	

Table 8. The number of patients with applied blood transfusion

It is observed that the bleeding occurred in patients of gestational age ≤ 32 weeks, and in other patients it did not occur. However, statistical analysis showed no significant difference between groups. Table 9 provides information

about the time of administration blood transfusions to patients which had an intracranial hemorrhage. 50% of these patients received blood transfusion in the first week of life, which is statistically significant ($P = 0.000$) in terms of association between intracranial hemorrhage and transfusion applications in the first week. However, this pattern is not sufficiently representative for the adoption of concrete conclusions, because of small number of such patients.

GD (weeks)	Bleeding	Blood transfusion in the first week	Blood transfusion in further treatment	P-value
≤32	10	5	5	0.000

Table 9. The connection of bleeding with the application of blood transfusion in the first week

In the group of patients ≤ 32 weeks of gestational age, iron is introduced into therapy on average 34th day of life, while in second group of patients, it began on average on 32th day (Table 10). There was no statistically significant difference between the two groups in term of iron therapy.

GD (weeks)	Average (day)	SD	Min (day)	Max (day)	P- value
≤32	34	11	18	60	<0.965
33-37	32	5	26	35	

Table 10. The beginning of iron therapy

There was a statistically significant difference ($P < 0.005$) in the length of treatment in patients of gestational age ≤ 32 weeks and those of gestational age 33–37 weeks (Table 11).

GD (weeks)	Average (day)	SD	P- value
≤32	27	22	<0,005
33-37	14	10	

Table 11. The length of treatment

5. DISCUSSION

Anemia of prematurity is the focus of clinical trials in the last decade, with still uncoordinated approach, moving from observational approach and occasional controls of hematological status, limited use of erythropoietin, to liberal or today more often, restrictive practice of transfusion of packed RBCs. Based on research conducted in recent years, protocols are established, which include in evaluation the level of hemoglobin, the level of respiratory disease and the traditional signs and symptoms of pathological anemia. In this study, the premature infants are divided into two groups based on gestational age. Premature infants of gestational age ≤ 32 weeks (62 % of patients) were in the first group, while premature infants of gestational age between 33-37 weeks (38 % of patients) were in the second group. The division is modeled on other studies, which state that the anemia of prematurity is significantly more pronounced in infants gestational age ≤ 32 weeks, compared to the rest of preterm infants. Cassady G. and Rosenkrantz T. (5) state that a half of prematurely born children, who belong to this group, develop anemia, as it typically does not occur in children of gestational age of 33-37 weeks. In a similar way, a study

by Wardrop and associates was done (6), with the difference that, they are the second group divided into two, where one did infants gestational age 33-35 weeks, and the other infants gestational age 35-37 weeks.

The birth weight was measured for all premature infants and there was a significant difference among two groups, as it was expected. In the first group average birth weight was 1.394 g, while in the second group, it was 2.242 g (Table 2). This parameter was taken into account as one of the risk factors for anemia of prematurity, because there is a connection between low and very low birth weight and early occurrence of serious anemia (2, 3, 7).

As regards APGAR score, values in the first and fifth minute were taken into account and significant statistical difference has been noticed. In the first group, average APGAR score in the first minute was 5.56 while in the fifth minute it was 6.5. In the second group, there were less variations, so the average score in the first minute was 7, while in the fifth minute it was 7.67 (Table 3).

Among 100 patients, 21 % died. In the first group of patients there were 27.42 % deaths, while in the second group number of deaths was significantly lower. Namely, only 10.53 % of premature infants with gestational age between 33-37 weeks died. Statistical analysis has shown significant difference in terms of mortality among these groups (Table 4.). These results correlate with the results of a study by Banarjee J. and associates (7), which show a significantly higher infant mortality gestational age ≤ 32 weeks, compared to the rest of preterm infants.

In addition, patients in the first group had, on average, a longer stay at the Pediatric Clinic in relation to another group. The average length of treatment, patients from the first group, was 27 days. Patients in the second group, on average, spent 14 days on treatment (Table 11). Hintz S. et al. (8) also indicate a significant difference in the length of treatment between infants small for gestational age and very low birth weight, compared to the rest of preterm infants. We found a statistically significant difference in length of treatment between the two groups ($P < 0.005$).

Focus of the research was hematology status and blood transfusion needs. At the admission, the first and second group had approximately same values of blood count which has been changed significantly during hospitalization, meanwhile blood transfusion needs arise. So the average number of erythrocytes in the first group was $4,39 \times 10^{12}$, hemoglobin value was 155 g/L and average hematocrit was 0,49 L/L. In the second group results were similar: average number of erythrocytes in the second group was $4,52 \times 10^{12}$, hemoglobin value was 167 g/L and average hematocrit was 0,51 L/L. Statistical analysis has proven significant difference in number of erythrocytes among patients of gestational ≤ 32 weeks and patients of gestational age between 33-37 weeks ($P < 0,003$). However, there was no significant difference in hemoglobin and hematocrit level among groups of patients (Table 5, 6 and 7). Banerjee J. et al. (7) did a study association of hemoglobin after birth with short-term outcome of treatment

prematurely born infants. They proved its connection with the subsequent need for transfusions and death.

Among 100 patients, 21 % required blood transfusion during the treatment. In the group of premature infants of gestational age ≤ 32 weeks, 29.03 % received blood transfusion. In the second group, 7.9 % of patients required blood transfusion during hospitalization at Clinic (Table 8). Statistical analysis showed significant difference in blood transfusion needs among premature infants of gestational age ≤ 32 weeks and premature infants of gestational age between 33-37 weeks. Strauss R.G. (9) states that transfusions annually receive even 300.000 premature infants, but mostly, it is about infants with very low and extremely low birth weight.

In the group of premature infants of gestational age < 32 weeks even 29.3 % received transfusion of erythrocytes, while in the group of premature infants of gestational age between 33-37 weeks, only three of them received transfusion of erythrocytes. Statistical analysis has proven significant difference ($P < 0,01$) among these groups in terms of need for blood transfusion.

Zuppa and coworkers (10) worked on study about connection of gestational age and blood transfusion needs. They have proven that premature infants of gestational age ≤ 32 weeks are the most probably candidates for blood transfusion and that is in accordance to our findings.

Interesting data was arisen during the research of connection between occurrence of intracranial bleeding and blood transfusion application. Namely, among 18 premature infants of gestational age ≤ 32 weeks, in 10 of them intraventricular hemorag were registered. In contrast, among 3 premature infants of gestational age between 33-37 weeks, there was no such bleeding. However, because of small number of cases, statistical analysis did not show significant difference among groups.

Due to intracranial bleeding associated with the application of transfusions in the first week of life, it is made the examination of these data in the first group of patients. Namely, Christensen R. D. (11) associated the occurrence of intracranial bleeding with early application of transfusions, indicating that the subsequent application is associated with the occurrence of necrotizing enterocolitis.

Goldber and coworkers (12) show the possibility of bleeding caused by rapid growth of intravascular volume in premature infants of gestational age ≤ 32 weeks. And other studies confirms connection between intraventricular hemorag and blood transfusion of deplasmated erythrocytes in premature infants (13, 14, 15).

Among 10 patients with intracranial bleeding in the group of premature infants of gestational age < 32 weeks, 50 % of them received blood transfusion in first week of life and other 50 % received blood transfusion later during hospitalization. Statistically there was significant connection ($P = 0.000$) of occurrence of intracranial bleeding and blood transfusion application in first week of life. Since intraventricular hemorag has multifactor etiology which includes fluctuations of cerebral flow and increase of cerebral venous pressure and taking into ac-

count that small number of patients were in place, this sample is not enough representative for making concrete conclusions, although surely indicates the connection noticed by other authors as well as need for further research of this connection in more relevant sample.

Finally, there were collected the data about the time of beginning the iron therapy, during the stay of patients at the Clinic. In the first group of patients, iron therapy was administered on average 34th day of life, and in the second group on average on 32th day. There was no statistically significant difference between the two groups in term of iron therapy (Table 10).

Meyers P. et al. (16) reported that the timely beginning of iron therapy is necessary to stimulate erythropoiesis in premature infants, since the iron depots are established in the third trimester of pregnancy, in order to avoid anemia due to iron deficiency, since it is known that anemia of prematurity does not correspond to the iron therapy.

6. CONCLUSIONS

Frequency of anemia with drastic fall of hemoglobin and hematocrit and need for blood transfusion in premature infants with gestational age < 32 weeks, is 29.3 %, meaning that almost every third premature infant of gestational age < 32 weeks develops anemia requiring treatment.

There is statistically significant difference in frequency of anemia in premature infants of gestational age < 32 weeks compared to premature infants of gestational age > 32 weeks, meaning that level of anemia negatively correlate with gestational age.

There is a significant difference in birth weight and APGAR score between premature infants of gestational age ≤ 32 weeks and premature infants of gestational age between 33-37 weeks, which indicates worse condition of these children at birth and more aggressive approach during laboratory analysis, which makes influence to earlier development of anemia.

There is no significant difference in the blood count of preterm infants at admission in relation to gestational age.

Premature infants of gestational age ≤ 32 weeks due to frequent development of manifested anemia during hospitalization, more often requires blood transfusion during treatment what is statistically significant.

Premature infants of gestational age ≤ 32 weeks have risk of occurrence of posttransfusion complications, while the most serious one among them is intracranial hemorag connected to application of blood transfusion in first week of life.

• Conflict of interest: none declared.

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