Erythropoietin versus Restrictive Transfusion Guidelines

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Abstract

The article contains recent data concerning pathophysiology of prematurity anemia, emerged from two clinical studies conducted in the Polizu Department of Neonatology.
Aims: *Finding new ways to decrease the number of transfusions for anemic premature babies admitted in Polizu Intensive Care Unit.*
Methods: *In 1998, for the first time in Romania, erythropoietin was used as an alternative therapy in anemia of prematurity, in the neonatal intensive care unit of the Maternity of Polizu.*
The controversies regarding erythropoietin use in treatment of preterm anemia led to two clinical trials. The first one, conducted in 2001, aimed the effect of erythropoietin in reducing the number of transfusions. The study enrolled 126 preterm babies less than 32 weeks gestation and 1,500 g birth weight; 63 were treated with erythropoietin (EPO) and other 63 - control group, without EPO treatment.
The second study, finalized in 2008, tried to ascertain the effect of more restrictive transfusion guidelines in 54 premature newborns not treated with EPO.
Results: *Both studies showed an important decrease in the number of transfusions required. In 1998-2001 the mean transfusion number for preterm births that did not receive erythropoietin was 4.9 compared to 3.2 for the EPO (+) group (p=0.01 C.I. 95%). In 2008 the number of transfusions decreased even more, the mean number of transfusions being 1.9 (p=0.001, C.I. 95%).*
Conclusions: *Data emerging from both studies demonstrate that improved preterm care, as well as more restrictive transfusion guidelines, is more important in reducing the number of transfusions than EPO therapy.*
The number of transfusions and transfused volumes were significantly lower when more restrictive red blood transfusion guidelines were applied, compared to EPO treatment.
Keywords: *anemia, prematurity, erythropoietin, transfusions, guideline*

Background

The anemia of prematurity (AOP) is one of the main diseases treated with packed red blood cell transfusions in hospitalized patients.

Histopathological aspects: AOP is a normochromic, normocytic, hiporegenerative type of anemia, characterized by:

- low levels of plasma erythropoietin;
- reduced blood volume;
- insufficient erythropoiesis;
- iatrogenic blood loss.

AOP was long time thought to be nutritionally insensible, but iron, folic acid and vitamin deficiencies (E, B1) aggravate anemia.

Erythropoietin is the most important hormone which regulates erythropoiesis and the main erythropoietic organ in fetuses and newborns is the liver.

AOP is most common in preterm births with a gestational age below 32 weeks. Hemoglobin nadir is reached at 4-10 weeks postnatal age. The mean value of hemoglobin is 10 g/dl for newborns with birth weights between 1,200 g and 1,400 g and of 6-9g/dl for those below 1,200 g.

There are three mechanisms involved in the pathology[1,2,3]:

1. inadequate red cell production;
2. shorter red blood cell survival and hemolysis;
3. iatrogenic blood loss resulting from blood sampling.

1. Inadequate red blood cell production

In preterm births, erythropoietin is mainly synthesized in the liver which is relatively insensitive to hypoxic injuries when compared to the kidney. As a result, erythropoietin production may not be stimulated until the hemoglobin levels reach 6-7 g/dl. In extremely low birth weight infants the red blood cell production is delayed even in severe anemias.

Moreover, erythropoietin has a high distribution volume and is rapidly eliminated by newborns, shortening bone marrow stimulation time.

Erythrocyte precursors in preterm births are sensible to erythropoietin action when this growth factor is endogenously produced or administered, but the response is delayed if iron stores are low[4,5].

Anemia increases the erythropoietin level and the reticulocyte count, but rapid weight growth is strongly associated by an adequate increase in hemoglobin concentrations.

Reticulocyte response is not always concurrent with the spontaneous increase of hemoglobin and hematocrit, and cannot be used as a predictor for anemia recovery[5]. Moreover, transfusions can inhibit erythropoiesis and stimulate plasma-free hemoglobin synthesis. Plasmatic reticulocytes and erythropoietin levels decrease 7 days after the transfusion and normalize after 14 days[6].

2. Shorter red blood cell survival and hemolysis

Neonatal mean red blood cell life is two thirds of an adult's erythrocyte life. For most very low birth weight preterm births, erythrocyte life is only 35-50 days. This is caused by many factors including: HbF, decrease of intracellular ATP and carnitine levels, low enzyme activity, high susceptibility to lipid peroxidation and cellular membrane damage[7,8].

3. Iatrogenic blood loss

Frequent blood sampling can result in a loss of 5-10% of total blood volume. The quantity and frequency of blood sampling influences the severity of anemia.

In a typical 800 g birth weight premature infant, with red cell mass at birth of 27 ml, avoidance of blood transfusion depends on avoidance of blood loss.

Prophylaxis and treatment of anemia of prematurity

Prophylactic methods to prevent and reduce the severity of anemia[1,2,3] and to diminish the risk of multi-donor transfusions and complications:

- Late cord clamping.
- Restriction of blood sampling.
- Erythropoietin prophylaxis.
- Enteral or parenteral feeding with and appropriate uptake of proteins and calories.
- Vitamins and iron supplementation.
- Safe, single donor transfusions.
- Collecting and transfusing cord blood (autolog transfusion).

Recombinant human erythropoietin (rhu-EPO) is successfully used[9,10,14] in the treatment of different forms of anemia. In vitro studies showed that the main etiology of anemia of prematurity is the low level of plasmatic erythropoietin.

Pharmacokinetic research demonstrate that preterm births need high levels of erythropoietin because of its distribution volume and rapid elimination[4]. Several studies showed that erythropoietin doesn't modify transfusion number in the first 2 weeks of life, especially in very ill preterm births. Recent reports focus on early administration, in the first week of life, in order to reduce anemia caused by iatrogenic losses and to prevent anemia of prematurity[15].

Even though in the past 15 years a lot of information about the erythropoietin use has become available, there is still much of controversy. Advances in the management of extremely low birth weights reduce the number of transfusions. Most likely, erythropoietin associated with more restrictive transfusion guidelines and in parallel with the decrease of blood sampling volumes will have the highest impact in reducing the transfusion requirements in preterm births[13].

Red blood cell transfusions[11,12,13,17,18]

Ninety percent of infants weighting less than 1,000 g or less than 28 weeks gestation at birth require multiple small volume PRBC transfusions, sometimes of high importance in preventing the effects of anemia. The hemoglobin levels indicative for blood transfusion and the definition of „non-physiologic" versus „physiologic" anemia in preterm infants is fraught with controversy. Transfusion guidelines differ from an intensive care unit to another, depending on birth weight, gestational age and severity of the illness. The desire to limit exposure to multiple donors has led to a lower hematocrit trigger for transfusions consensus being reached.

Enteral iron supplementation[16,19] is necessary for effective treatment of AOP. Oral iron supplementation mainly ranges between 2 and 6 mg/kg daily. Several studies have found hypocromic erythrocytes (evidence of iron-deficient erythropoiesis), in rhu - EPO treated, oral iron-supplemented premature infants compared with iron-supplemented control.

Clinical studies on the anemia of prematurity

Background

Incidence of prematurity in the Neonatology Department of IOMC "Polizu" Maternity is 1313 % in the last 10 years, approximately 4% of births being represented by infants with a gestational age below 32 weeks.

Anemia of prematurity is one of our frequent pathologies. We are trying to limit the number of transfusions by elaborating more restrictive, case - adapted guidelines. In 1998, erythropoietin therapy was started on infants below 32 weeks gestational age and 1,500 g birth weight in order to prevent anemia of prematurity.

Seven years later, in 2008, a second study was conducted in order to observe the impact of improved levels of care and intensive care protocols on this particular pathology.

Patients and methods

The data was collected and analyzed using the Epi Info 2000 (version 6.04) and, respectively, the Epi Info 2008 (version 3.5.1) statistical analysis software.

In 1998 was started a three year prospective study (1998-2001) assessing the role of erythropoietin in preventing anemia of prematurity.

The study enrolled 126 preterm births with a gestational age below 32 weeks and birth weight <1,500g, with hemolytic or hemorrhagic disease, congenital anemia, congenital malformations or infections (TORCH), IVH > gr.II, chronic pulmonary disease, NEC, sepsis:

EPO Group - 63 patients - EPO (+)

Control group - 63 patients - EPO (-)

Table 1

Inclusion/exclusion criteria

Inclusion criteria
- Preterm births ≤32 weeks GA (26-32wks)
- Birth weight less than 1500 g (650 – 1500 g)

Exclusion criteria
- Anemia at birth (Htc<45%, Hb<13 g/dl)
- Hemolytic disease
- Hemorrhagic disease
- Intraventricular hemorrhage >2nd degree
- Congenital malformations
- Congenital infections (TORCH)
- Chronic pulmonary disease
- Sepsis, NEC

Ideal conditions
- good pregnancy follow-up
- Dexamethasone prophylaxis
- delayed clamping of the umbilical cord
- Surfactant treatment of neonatal idiopathic RDS

Mandatory
- Lowering sampled blood volumes
- restricted transfusions of PRBC (Packed Red Blood Cells)

The administered treatment was as follows:

First dose: day 15;

Amount: 300 IU/kg;

Frequency of administration: 2 doses per week;

Duration of treatment: 6 weeks;

Administration route: subcutaneous.

Complementary treatment:

- Iron supplementation: An oral suspension of iron hydroxide polymaltose complex was used. The initial dose of 2 mg/kg/day was raised to 6-8 mg/kg/day if plasma iron dropped below 60 mg/dl, especially for preterm births treated with erythropoietin, knowing that human recombinant EPO accelerates erythropoiesis, thus increasing the need for iron.
- Folic acid supplementation: 1 mg/week p.o.

Table 2

Monitoring during erythropoietin therapy

Cardiorespiratory	Daily (HR, RR, BP)
Blood count and indices	Day 1,7,14,21,28,35,42
Plasmatic iron	Day 14,21
Head ultrasounds	Day 1,3,7,14
Ophthalmologic exam	1 month of age
Iatrogenic infections	Central and peripheral cultures-weekly
Necrotizing enterocolitis (NEC)	feeding tolerance Stool culture XRay
Anthropometric measurements	Weight, height, head circumference
Blood sampling	Total amount and ml/kg
No of transfusions	Day 1-14, 15-28, >28th day
Adverse effects	High blood pressure, neutropenia, infections

HR - heart rate, RR - respiratory rate, BP - blood pressure

Table 3

Transfusion guideline in first study (1998-2001)

Need for mechanical ventilation FiO2 >40%	No need for mechanical ventilation	associated conditions
Htc <40% Hb <14g/dl	Htc <35% week 1, 2 Htc <30% week 3, 4 Htc<25% >week 4	Cardiac failure Apnea Increase of oxygen need over 20% in 24 hours Tachycardia (>160bpm over 24hrs) Failure to thrive (>4days) Acute blood loss

Table 4

Results that can be associated with erythropoietin treatment in the first study

	EPO (+)	EPO (-)	P value
BW (g)	1306 +/-316	1296+/-299	0.96
GA (wks)	29.8	29.9	0.86
Hb at birth	16	15.5	0.4
RDS	34	26	0.6
Surfactant	14	8	0.05

Table 5

Hemoglobin variation and the transfusion requirements in the first study

	EPO (+)	EPO (-)	P value
Hb value day 42	9.3 +/- 1.8	8.4 +/- 1.5	.03
Total no. of transfusions	3.2 +/- 3	4.9 +/- 2.8	.01
Total volume of transfused blood (ml/patient)	38	85	.003

- Vitamin E supplementation - 25U/day p.o. (1mg vitamin E for 1 mg bivalent iron), with enteral feed rates exceeding 60 ml/kg/day.

The transfusion guidelines used are provided in table 3.

Results:

There were no statistically relevant results between the two groups regarding body weight (BW), gestational age at delivery (GA), hemoglobin value (in the first day of life), and the administration of surfactant (Table 4).

Hemoglobin curves showed a significant increase of Hb in day 42 for patients EPO (+) 10.2 ±1.8 g/dl compared to 8.4 ± 2.8 g/dl for patients EPO (-) p=0.003 (Table 5, Figure 1);

Total number of transfusions was 3.2 ±3 in EPO(+) patients compared to 4.9±2.8 in EPO (-) patients p=0.001 (Figure 2).

This study was reviewed in 2008 for evaluating the real efficiency of erythropoietin, considering the whole context of improved preterm care, less invasive monitoring and altered transfusion guidelines.

On this ground a new study on the anemia of prematurity was conducted, enrolling 54 preterm babies below 32 wks GA and below 1,500 gms BW, on the same inclusion/exclusion criteria. These preterm births did not receive erythropoietin (EPO -).

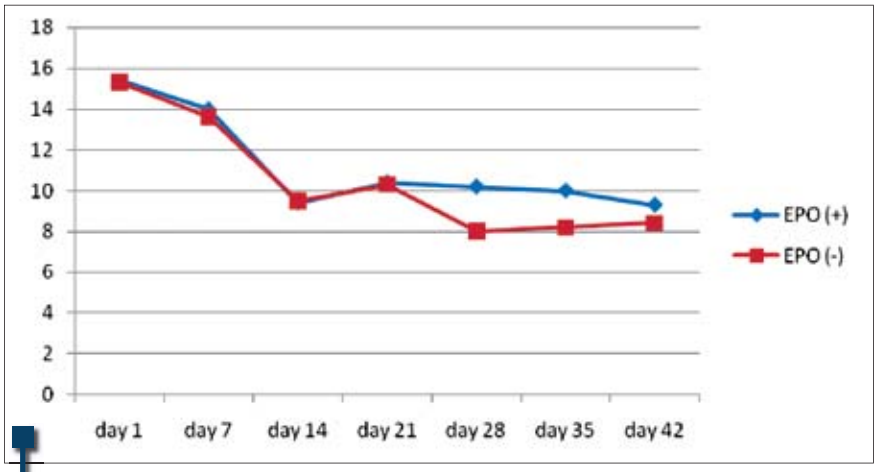

Figure 1. Hemoglobin curves for the first study

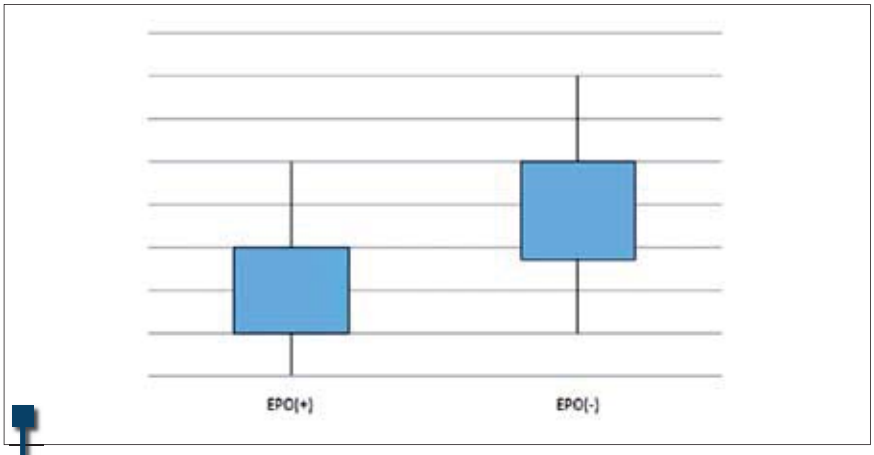

Figure 2. Total number of transfusions

Table 6

Transfusion guideline in second study - 2008

Htc ≤ 20% Hb < 7g/dl Ret < 4%	Htc ≤ 25% Hb < 8 g/dl	Htc. ≤ 39% Hb < 10g/dl	Ht ≤ 35% Hb < 12g/dl	Acute blood loss	Htc ≤ 30%
Any situation	~10 episodes of apneas/24 h ~2 episodes of bag ventilation/24 h T Tachycardia more then 24h(~180/min) and tachypnea (~80) Failure to thrive (<10g/day more then 4 days) Respiratory disease that needs > 25% hood oxygen/NCPAP/CMV	RDS >35% need for inspired oxygen	Severe RDS requiring MV and inspired oxygen >50%	Vascular refill	Presurgery

Table 7

Comparative results EPO (+)1998-2001 and EPO (-) in 2008

	EPO(+) 1998-2001	EPO (-) 2008	P value
BW	1350	1250	.05
GA	30	29	.25
Hb day 1	15.9	16.1	.49
MV	47%	66%	.09
MV duration	3.8	4.7	.16
Oxygen therapy duration	3.7	6.9	.007 ‡
IVH	88%	48%	.0001 ‡
ROP	2.3%	25%	.002 ‡
Nosocomial infections	58%	44%	.21
Antibiotic therapy duration	16	19	.29

‡ Statistically significant, p< 0.01

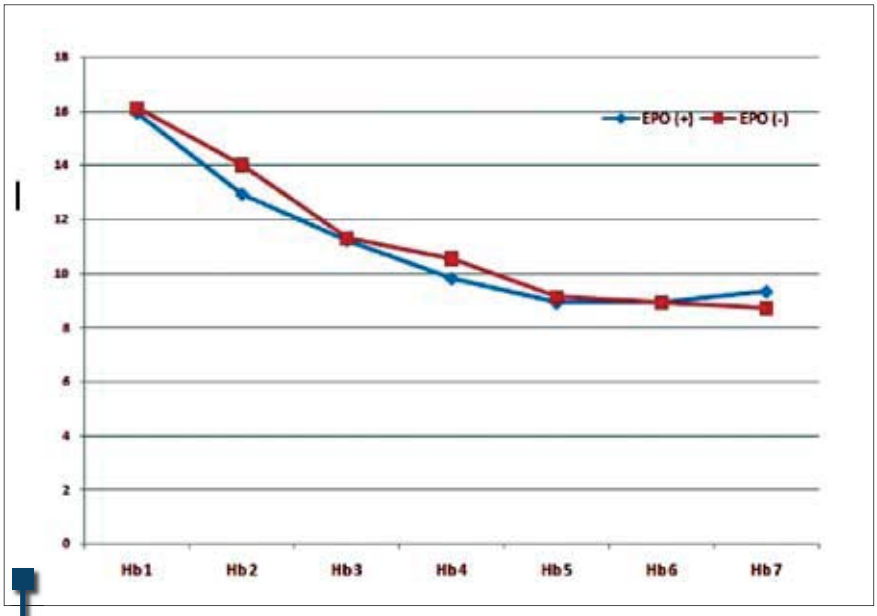

Figure 3. The mean hemoglobin value in the 42nd day of life

The same orally administered iron suspension was used, with the same dosage and administration criteria. Vitamin E and folic acid supplementation were no longer used.

A modified transfusion guideline was used (Table 6).

Monitored parameters:

- Hemoglobin and hematocrit curves;
- Reticulocyte response;
- Blood sampling volumes;
- Number of transfusions and transfused blood volume;
- Values of hemoglobin and hematocrit before transfusion;
- Curves of caloric and protein intake.

The results obtained were compared to those of 63 preterm births that received erythropoietin (EPO+) during the first study (1998-2001).

The data was analyzed using the Epi Info 2008 (version 5.3.1) software.

Results of 2nd Study

There were no statistically significant differences in the two groups for gestational age, birth weight, Hb in the first day of life.

A lower incidence of periventricular/ intraventricular hemorrhage was noticed for the EPO (+) group, together with an increase of retinopathy of prematurity, paralleling the 2004 onset of ROP diagnosis and treatment national program. No important differences of hemoglobin values were observed in the two groups.

The mean hemoglobin value in day 1 was 16.1 g/dl in the EPO (+) group and 15.9 g/dl for the EPO (-).

In the 42nd day of life the mean hemoglobin value was 9.3 g/dl for the EPO (+) group and 8.7 g/dl for the EPO (-) group (Figure 3).

There is an increased reticulocyte response in preterm births receiving erythropoietin one week from the first dose reaching a peak in day 42 (Figure 4).

For the EPO(-) group there is a decrease in reticulocyte response starting in week 4.

Mean blood sampling volume was 12 ml in the EPO (-) group compared to 14 ml for the EPO (+); the number of transfusions increased with the increase of blood sampling volumes, p=0.01.

The mean number of transfusions was significantly different in the two groups: 3.2 transfusions for the EPO (+) group and 1.9 for EPO (-) (p=0.001).

A dramatic decrease of transfusions can be observed. In 1998 the mean number of transfusions for preterm births that did not receive erythropoietin was 4.9 compared to 3.2 for the EPO (+) group. In 2008 the number of transfusions decreased even more, the mean number of transfusions being 1.9 (P<0.01) (Figure 6).

This proves that better preterm care, as well as more restrictive transfusion guidelines, is more important than erythropoietin therapy in reducing the number of transfusions.

There are no significant differences in the mean values of hemoglobin before transfusion: 8.6 g/dl in the EPO (+) group and 7.7 g/dl for the EPO (-) group (p=0.11) .

Statistically significant differences for mean hematocrit levels were noticed: 28% in the EPO (+) group and 24% in the EPO (-) group (p=0.02) .

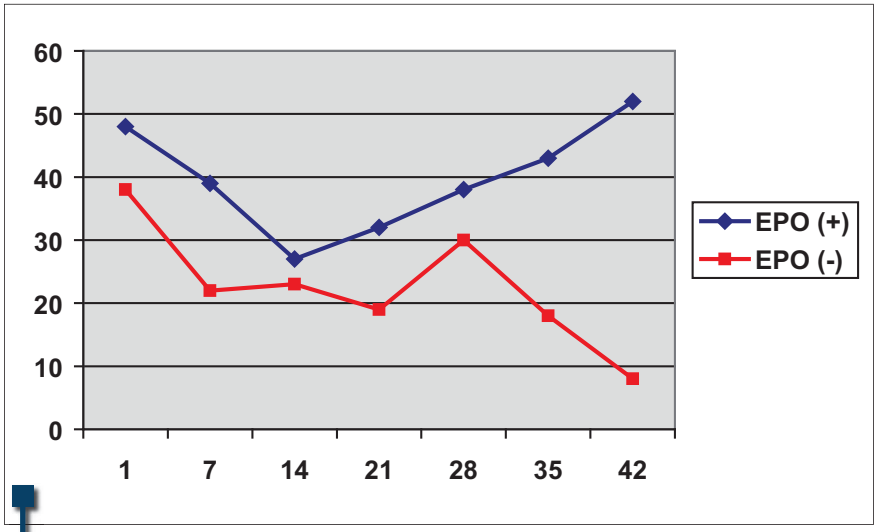

Figure 4. Reticulocyte response

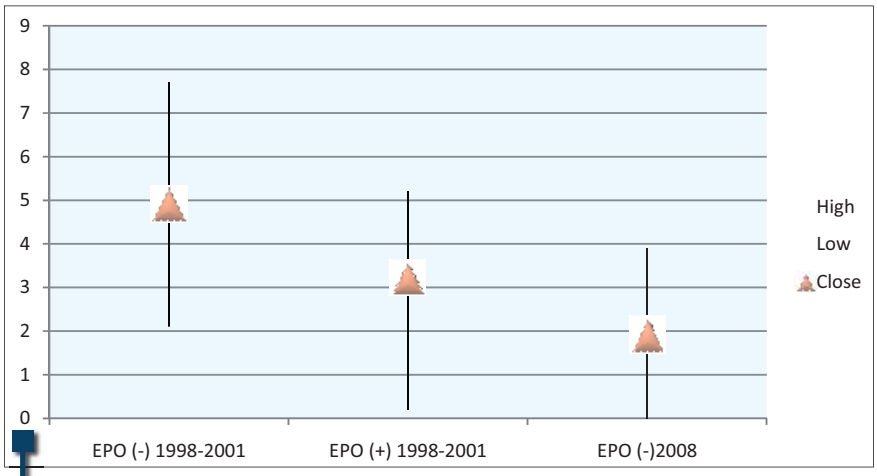

Figure 5. Compared PRBC transfusions

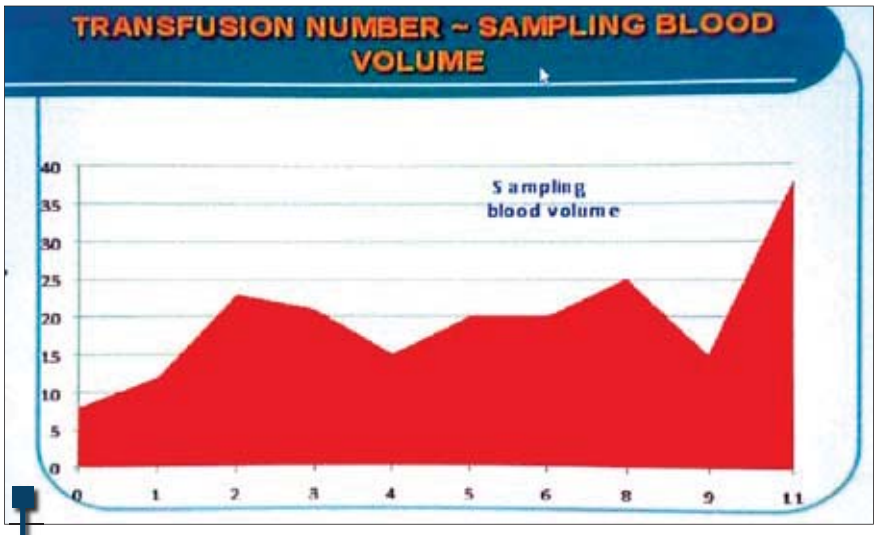

Figure 6. Mean number of transfusions (1.9)

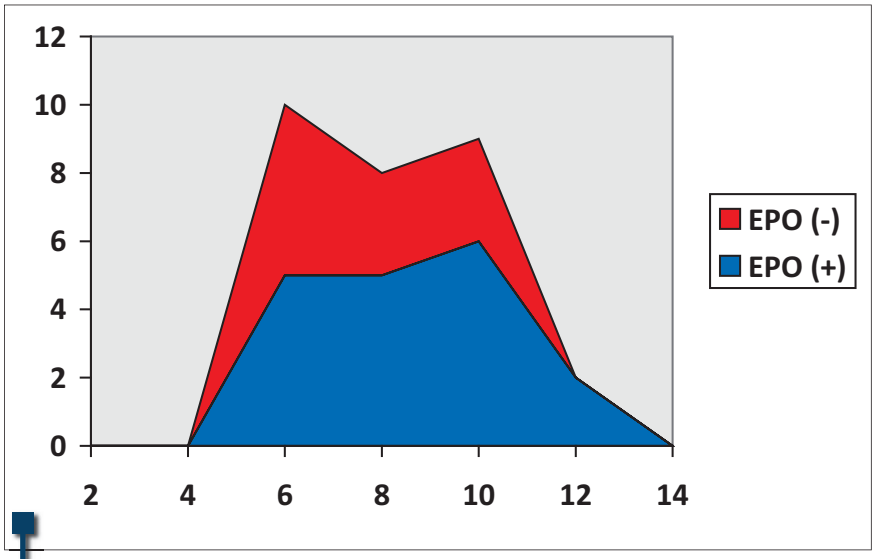

Figure7. Mean hemoglobin values before transfusion

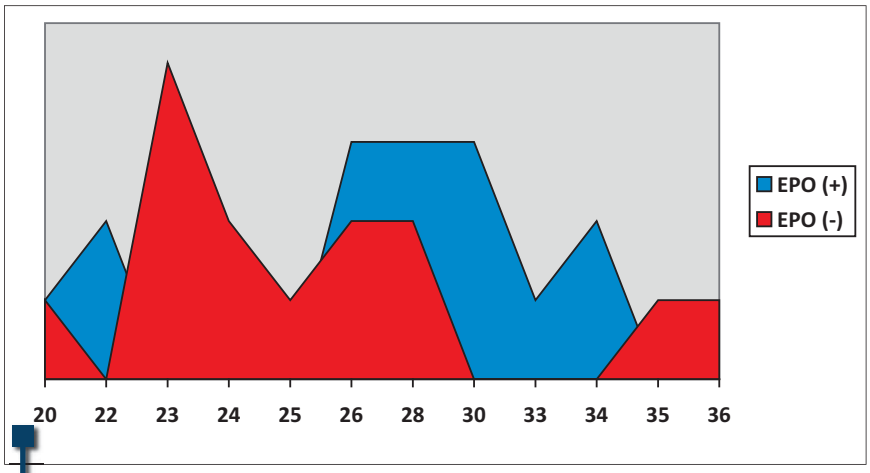

Figure 8. Mean hematocrit levels before transfusion

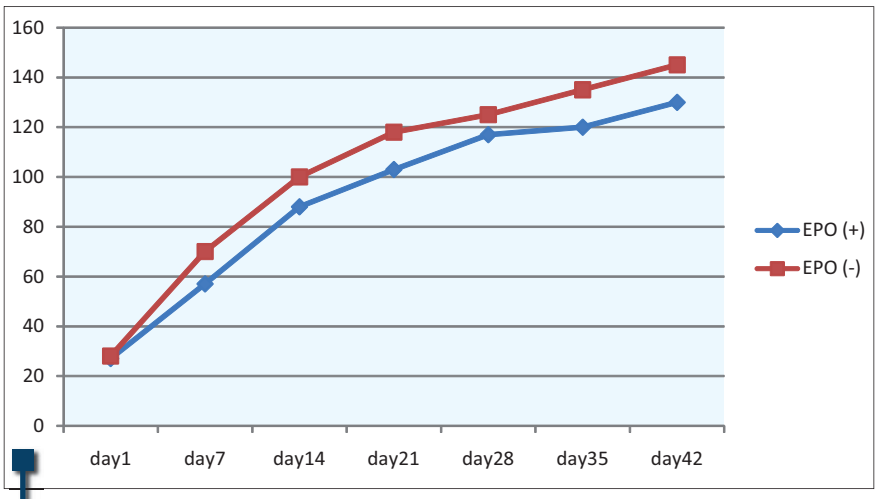

Figure 9. Calorie intake curve - 2001

In 2008 better caloric and protein intake curves are observed (Figure 9, Figure 10).

Discussions

The above-mentioned studies have been conducted a few years apart. During the last 10 years preterm care techniques and technologies (mechanical ventilation, nutritional support, monitoring) were updated, with a poignant tendency towards non-invasiveness.

Also, the conception on nutritional support has been changed, aiming to early minimal enteral feeding and higher caloric parenteral nutrition. All of the above are strong reasons for designing new studies on erythropoetin therapy.

Ten years ago we started erythropoietin use for premature anemia, based upon several scientific reports proven efficacy. At that time anemia of prematurity was included in a national health care program, receiving fluctuating financial support. Therefore, erythropoietin therapy did not cover the entire population of premature, eligible newborns during 1998-2001.

Although the 1998-2001 study results were significantly in favor of erythropoietin use, with a subsequent decrease of transfusion number from 4.9 to 3.2. Program completion also ceased erythropoietin prophylaxis and treatment in premature anemia in our unit.

Meanwhile, the interest for decreased transfusion rate remained constant. Modern, non-invasive monitoring techniques, together with micro-sampling devices, granted sample limitation (both number and blood volumes) from 14 ml/kg to 12 ml/kg, with a neat correlation between sampling volume and number of transfusions (p=0.01).

Decreasing mean pre-transfusion hematocrit levels from 28% to 24% (p=0.02) was also an important factor; in 2008 the number of transfusions decreased even more, towards an average of 1.9 (p=0.001).

Also, the conception on nutritional support has been changed, aiming to early minimal enteral feeding and higher caloric parenteral nutrition.

A more generous protein and caloric intake was allocated: 3.5 g/kg and 120 cal/kg (2008), compared to ~2.6 g/kg and ~100 calories/kg (1998 - 2001) in DOL 21.

Conclusions

Both the number and the volume of transfusions were significantly lower when more restrictive blood transfusion guidelines were applied, compared to those used in association with erythropoietin prophylaxis.

When evaluating the efficiency of erythropoietin therapy in very low birth weight (VLBW) premature infants, mirrored by the number and volume of transfused blood products, one should carefully consider the coexisting impact of the more restrictive transfusion guidelines. These guidelines could have a similar impact with erythropoietin administration on transfusion procedures of very low birth weight infants.

For a proper evaluation we need to reconsider erythropoietin administration together with more restrictive transfusion guidelines and lower iatrogenic losses.

A good collaboration with the Hematology Department is crucial in order to lower the exposure to multiple donors. ■

Legend:
AOP - anemia of prematurity
EPO - erythropoietin
Hb - hemoglobin,
Htc - hematocrit,
ICU - Intensive Care Unit
NEC- Necrotizing enterocolitis
RBC – red blood cell
RDS – respiratory distress syndrome
VLBW - very low birth weight

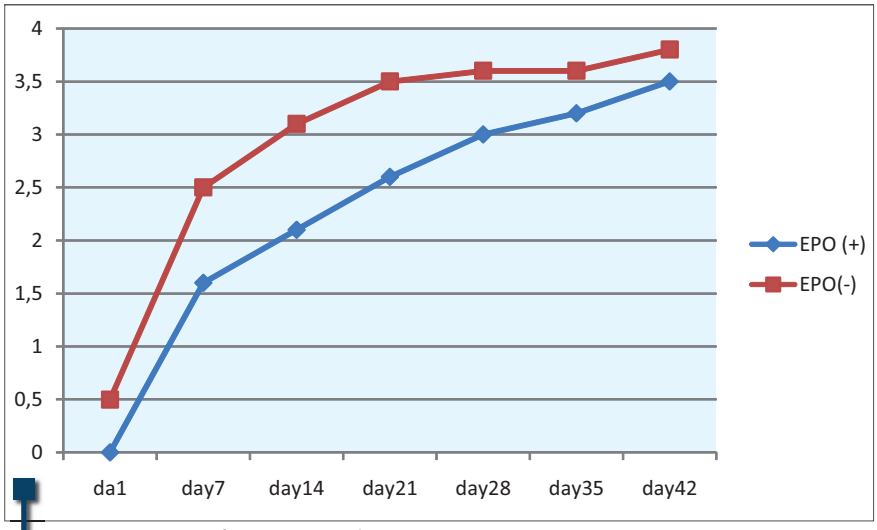

Figure 10. Curves for protein intake - 2008

Table 8

Anemia of prematurity - statistical data

VARIABLE	EPO (+) 1998-2001	EPO (-) 2008	P value
Sampling blood volume (ml/kg)	14	12	0.009‡
Hb day 28	8.9	8.9	0.8
Htc day 28	28	28	0.7
Ret.day 28	33	18	0.02†
Hb before transfusion	8.6	7.7	0.11
Htc before transfusion	28	24	0.02†
Mean transfusion number	3.2	1.9	0.001‡
Mean RBC volume (ml/kg)	43	28	0.05

Hb - hemoglobin, Htc - hematocrit, RBC - red blood cell;
† Statistically significant p<0.05; ‡ Statistically significant p<0.01

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