

ANEMIA OF PREMATURITY MANAGEMENT IN THE TERTIARY NEONATOLOGY CENTRE OF CLINICAL EMERGENCY COUNTY HOSPITAL CONSTANTA

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ABSTRACT

Objective: Preterm neonates represent a category of neonates at high risk for anemia. Due to particular pathologic processes and clinical presentation in preterm neonates, this type of anemia is described as a separate entity named anemia of prematurity (AOP). The population represented by very low birthweight (VLBW) neonates is at the highest risk of developing anemia of prematurity. Reduced tissue oxygenation due to anemia can have short-term consequences (growth restriction, apnea episodes) or long-term consequences such as delayed neurological development, rapid detection, and management of AOP is needed to avoid its complications.

Material and methods: We describe the particularities of this condition and the interventions for its prevention or correction in a group of premature infants born at less than 32 weeks of gestation discharged home during 2021.

Results: We assessed the presence of anemia and the need for erythrocyte transfusion in 32 VLBW neonates, separated into two groups based on the gestational age: 24-29 gestational weeks (GW) and 30-31 GW. The number of neonates receiving a transfusion and the number of transfusion events was higher in the former; more immature group. We also identified more significant phlebotomy losses in the first group, contributing to a higher proportion of AOP cases needing erythrocyte transfusion.

Conclusions: Although our protocols for transfusion at this moment recommend lower hemoglobin thresholds, we tend to transfuse above those levels based mainly on clinical signs and symptoms. We need better prevention strategies for AOP, both by using cord blood and more strict monitoring of phlebotomy losses.

Keywords: anemia of prematurity, preterm neonates, very low birth weight, erythrocyte transfusion

Introduction

Anemia represents the impossibility of providing oxygen requirement for tissues by circulating red blood cells. In the newborn, slow erythropoiesis can lead to low hemoglobin/erythrocyte count levels without causing clinical consequences. The definition of pathological condition (anemia) and the need for therapeutic intervention (erythrocyte transfusion) should therefore be based on information on the status of newborn oxygenation, not just on hemoglobin or hematocrit, a fact that influences the current recommendations for newborn erythrocyte

transfusion (1).

The three major causes of anemia (through loss, by hemolysis, and insufficient production) combine to varying proportions in preterm newborns, generating "anemia of prematurity" which is the most common anemia of the newborn. Anemia of prematurity is a normocytic, normochromic anemia that affects most newborns with gestational age below 32 weeks, with a poor influence of iron or vitamin administration (2). It can be considered a variant of the physiological anemia of the infant where the hemoglobin levels reach a nadir of around 11 g/dl between 8-12 weeks of age (3). The AOP has lower levels of

hemoglobin (7 g/dl in some neonates), and we can observe it as soon as 4-8 weeks of age with the earlier presentation for the more immature neonates. For VLBW neonates, the nadir is reached before the corrected age of 40 weeks and will determine varying degrees of symptomatic hypoxia. Because AOP is symptomatic in most cases, it is not considered physiological and usually warrants rapid intervention (1,4).

The gold standard for the treatment of prematurity anemia is erythrocyte transfusion (5). It promptly corrects the deficit but also presents risks, especially hemodynamic risks and transmission of infections; therefore, we try to limit the number of transfusions. In addition, transfusion in itself, by downregulating the endogenous erythropoiesis, may be a cause of late anemia (6).

Treating prematurity anemia is a continuous challenge for the neonatologist, identifying clinical and paraclinical markers for anemia and stating the critical levels, to which the newborn should receive a transfusion. There is not a singular recommendation for the threshold levels of hemoglobin warranting an erythrocyte transfusion; two main approaches are presented in the literature – the “restrictive” (lower thresholds) and “liberal” (higher thresholds) for the hemoglobin levels when the erythrocyte transfusion is recommended (1,3,7). We summarize the criteria in Table 1.

Prophylactic measures which contribute

to reducing the number of transfusions, such as stimulating erythropoiesis and preventing/limiting blood loss, are also included in the current recommendations.

Material and methods

This retrospective study includes all preterm neonates born with a gestational age (GA) below 32 gestational weeks admitted to our intensive care unit and discharged home in 2021. We recruited a number of subjects, $n = 32$, and we separated them into two study subgroups based on their gestational age: subgroup 1 – neonates born before 30 weeks (14 subjects), and subgroup 2 – neonates born at 30-31 weeks (18 subjects). For all patients, we collected data regarding birthweight, gestational age, gender, duration of hospitalization, and corrected age at discharge. Clinical parameters we evaluated were: hemoglobin levels at birth and at the time of transfusion, number and timing of transfusion events, type of respiratory support when transfused, hemorrhagic events, and phlebotomy losses.

We compared the two groups in respect with the absolute number of transfusion events and the number of transfusion events by patient. We also analyzed the timing of the transfusion, type of respiratory support at the time of transfusion, and hemoglobin level when transfused. We analyzed transfusions in the early days <2 weeks of age,

Table 1. Recommendations for the erythrocyte transfusions in preterm neonates (1,3,7)

Recommendation	Liberal criteria (Hemoglobin g/dL)	Restrictive criteria (Hemoglobin g/dL)
Neonates: Receiving > 35% oxygen On CPAP or mechanical ventilation with MAP > 6-8 cmH ₂ O	15	12
Neonates: Receiving supplemental oxygen On CPAP or mechanical ventilation with MAP < 6-8 cmH ₂ O Presenting with significant apnea and bradycardia episodes (> 9 episodes in 12 hours, or 2 episodes in 24 ore needing PPV with bag and mask) during the treatment with methylxantines Presenting with HR > 180 b/min or RR > 80 resp./min with a duration of 24 hours Presenting with slow weight gain < 10 g/kg/day, 4 consecutive days while receiving 100 kcal/kg/day Undergoing surgery	13	10
Asymptomatic neonates with reticulocytes < 100.000/mm ³	10	7
CPAP – continuous positive airway pressure; MAP – mean airway pressure; PPV – positive pressure ventilation; HR – heart rate; RR – respiratory rate.		

between 2 – 4 weeks, and late transfusions > four weeks of age. We also separated the type of respiratory support into four classes: mechanical ventilation (MV), continuous positive airway pressure (CPAP), free-flow supplemental oxygen (O₂), and no respiratory support (w/o O₂).

We estimated the phlebotomy losses based on the written recommendations in the neonates' charts, assuming that 0.2mL were removed for each blood gas analysis, 0.5mL removed for each complete blood count analysis and biochemistry lab work, respectively, and 1mL for each blood culture.

Results

Table 2 presents the characteristics of the study groups.

Table 2. Characteristics of the patients included in the study

	GA<30w	GA >30w
No. of subjects	14	18
Male/Female	9/5	12/6
Mean BW (grams)	1107 (750-1450)	1606 (1160-2100)
Mean Hemoglobin at birth (g/dL)	15.73 (12.7-18.3)	15.56 (13-17.7)
Mean duration of hospital stay (number of days)	63.7 (37-104)	40 (25-84)
Number of transfused neonates	12/14	11/18
Transfusion events		
Total number	45	28
Average	3.75 (1-8)	2.54 (1-7)
Phlebotomy loss		
Average volume (mL)	15.57 (5.5-31)	8.86 (3-16.5)
Average percent	17.5	6.8

As expected, we had a more significant percentage of male subjects in the entire group (21/32, 65.62%), but the distribution between the two subgroups did not differ (64.28% below 30 weeks and 66.66% above 30 weeks). Average birthweight was lower below 30 weeks (1107gr and 1606gr, respectively). Hemoglobin levels at birth were similar, 15.73g/dL below 30 weeks and 15.56% above 30 weeks, close to those reported by other researchers (8).

During their stay in the hospital (which averaged 63.7 and 40 days, respectively), most neonates received at least one transfusion – 23

out of 32 (71.87%). Distribution of transfused neonates in the two subgroups was 12 neonates out of 14 born below 30 weeks (85.71%) and 11 neonates out of 18 born at more than 30 weeks (61.11%) as presented in Figure 1.

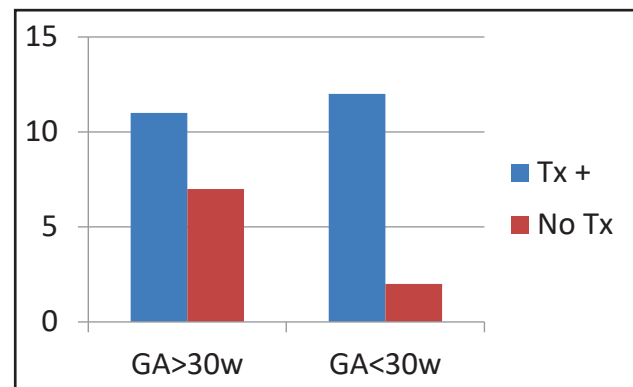


Figure 1 Distribution of the transfused neonates in the two subgroups.

Transfused neonates received between 1 and 8 transfusions, 73 total number of transfusion events, with 45 events in the neonates born before 30 weeks and 28 events in the neonates born after 30 weeks. The average number of transfusion events/patient was 3.75 and 2.54, respectively.

We analyzed the number of transfusion events and hemoglobin level in relation to the chronological age of subjects (Table 3).

Table 3 Correlation between transfusion events and chronological age.

	<2weeks	2-4weeks	>4weeks
Total No.	16	27	30
Average Hgb.	10,16 (9,3-14)	10,86 (8,8-13,3)	10,43 (8-12)
GA<30w	8	14	23
GA>30w	8	13	7

We observed that the highest number of transfusion events occurred at more than four weeks of age (30/73 – 41.09%). Conversely, the lowest number of transfusions were performed before two weeks of age (16/73 – 21.91%), and 27 transfusions were performed between 2 and 4 weeks of age (36.98%). Nevertheless, the majority of transfusions were performed before four weeks of age, when the cause of anemia is most probably an acute or subacute event and less probable true anemia of prematurity.

When we analyzed the distribution of the

transfusions in the two subgroups, we observed a marked difference in the number of transfusions performed after four weeks in the two subgroups. Neonates born before 30 weeks received 23 transfusions, while those born after 30 weeks only 7. This finding is probably influenced by a more extended hospital stay for the more immature neonates (37 days being the shortest stay), while the neonates born after 30 weeks are discharged sooner (25 to 84 days, with an average stay of 40 days). However, the average hemoglobin levels at transfusion were similar, regardless of the moment of transfusion.

When we analyzed the correlation between transfusions and type of respiratory support–Table no. 4 – we observed that roughly half of transfusions were performed while the neonates were independent of respiratory support (36/73 – 49.31%, 18 neonates in each subgroup).

Table 4 Correlation between transfusion events and respiratory support

	MV	CPAP	O2	W/o O2
Total No. Tx	13	10	14	36
Average Hgb.	11.6 (9.4-14)	11,63 (9-13)	10,31 (8.4-13)	10.2 (8-13,3)
GA<30w	8	7	12	18
GA>30w	5	3	2	18

For all other categories of respiratory support, we observed a higher number of transfusions in the <30 weeks subgroup. For these, we performed more transfusions while they had some respiratory support (27 transfusions) than when they did not need respiratory support (18 transfusions). Reversely, for the >30 weeks subgroup, fewer transfusions (10 transfusions) were performed while on respiratory support than without respiratory support (18 transfusions). This finding is probably influenced by the fact that neonates born after 30 weeks were more stable and needed less support compared with the immature ones. The hemoglobin levels at the time of transfusion were impacted by the type of respiratory support with patients on pressure support (mechanical ventilation and CPAP) with average levels of 11.6 g/dL and 11.63 g/dL, respectively. Hemoglobin levels were lower when subjects were transfused while without

pressure support, and we found only a slight difference in the hemoglobin levels, with an average hemoglobin of 10.31 g/dL for neonates with free-flow oxygen and 10.2 g/dL in those with no respiratory support.

We also analyzed the presence of additional causes of anemia. We identified seven neonates out of 14 in the group born before 30 weeks who had additional pathology that could be linked to anemia – four neonates had an intraventricular hemorrhage, one had a pulmonary hemorrhage, one had Methicillin-resistant *Staphylococcus aureus* sepsis (MRSA), and one had necrotizing enterocolitis. In the group of neonates born after 30 weeks, two neonates out of 18 had an intraventricular hemorrhage.

When we analyzed the phlebotomy loss (Table 1), we found a higher amount of iatrogenic blood loss in the neonates born before 30 weeks (on average 15.57 mL) and less (8.86mL loss on average) for the more mature ones. Moreover, when we compared the volume removed with an estimate of the blood volume at birth, the difference was even higher, with an estimated loss of 17.5% of the blood volume at birth in the neonates born before 30 weeks, compared with only 6.8% for those born after 30 weeks.

At discharge, all patients in the more immature group had anemia, and only two patients born after 30 weeks were discharged without anemia. According to chronological age, anemia was defined as a hemoglobin level of <13.4g/dL during the first month of life and <10.7g/dL after the first month.

Discussions and conclusions

Although in the entire group, male patients were predominant (21 male versus 11 female subjects), the distribution in the two subgroups was similar concerning the gender of subjects.

The percentage of the transfused neonates in our study was 71.87%, slightly higher than other studies show. It is estimated that 58% of the neonates with gestational age below 32 weeks

will receive at least one erythrocyte transfusion during their stay in the hospital, and the percentage increases to 90% when one considers only the ELBW neonates (5,6). In addition, we transfused at higher hemoglobin levels, using the

‘liberal’ criteria for the erythrocyte transfusions, which led to a higher number of preterm neonates being transfused during their hospital stay.

We can affirm that we treated with transfusions the preterm neonates not only for AOP but also for other types of anemia. However, since AOP is defined as anemia occurring between 4 – 8 weeks of age in preterm neonates (4) and we had the majority of the transfusion events before that age in our group, we could not clearly separate isolated AOP from other causes of anemia.

Phlebotomy losses play an essential role in the pathogeny of AOP. Especially for ELBW neonates, in the first weeks when they have a severe respiratory disease and frequent lab work, the phlebotomy losses can reach up to 10% of the blood volume and represent the most critical factor leading to AOP and the need for erythrocyte transfusions (9,10). In our group, the most immature neonates had significant iatrogenic blood loss, and the estimate could not account for repeated samples or other incidents. The reduction of repeated phlebotomies is crucial for preventing the rapid decrease of the circulating erythrocytes. Currently, we use micro techniques for most of our lab work, but the losses are still significant. Therefore, noninvasive monitoring techniques are needed to improve the control of iatrogenic blood losses (11).

The two patients with gestational age below 30 weeks (28 weeks/1200gr., and, respectively, 29 weeks/1300gr.) and no transfusion events during their hospital stay, had hemoglobin at birth above 18 g/dL (18.1 and respectively 18.3). This finding aligns with findings from other studies that emphasize the importance of prophylactic management measures, such as delayed cord clamping for preterm neonates (7,12). However, in our clinic, preterm neonates do not benefit consistently from delayed cord clamping. This study aims to improve our attitude and protocols to include this measure in the care of our preterm patients, being known that the delayed cord clamping in the preterm neonates correlates not only with the prevention of AOP and improvement in the iron status but also with a decrease in the incidence of intraventricular hemorrhage and late-onset sepsis (8,12).

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