

# Epidemiology, treatment and outcomes of anemia in premature newborn babies in Centre Hospitalier d'Essos, Yaounde, Cameroon.

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## Research article

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# Abstract

## Introduction

At birth, all newborns experience a decrease in hemoglobin levels; this decrease is more emphasized in premature babies. The objective of this work was to study the epidemiological, therapeutic and outcomes of anemia amongst preterm births in a reference hospital in Cameroon.

## Methodology

This was a two-year retrospective cohort study (January 1, 2016 to December 31, 2017). All premature infants with a hemoglobin level below 14g/dl at a given time of hospitalization were included in the study; these were divided into two groups: group A transfusion recipients and group B non-transfusion recipients. The main measurements were prevalence of premature anemia and incidence of blood transfusion, features of population and outcomes.

## Results

142 cases of anemic premature infants (56.34% female) with a mean gestational age of 31.58 +/- 2.81 weeks of amenorrhea and a mean birth weight of 1652.78 +/- 514.77g were included in the study. The prevalence of premature anemia was 24.2%. Blood transfusion was the most widely used therapeutic method with an incidence of 57.75%, followed by iron (56.34%) and Erythropoietin (EPO) (4.93%). Out of the 142 cases recruited, 82 were in the transfusion group and 60 in the non-transfusion group. Predictive factors of blood transfusion were gestational age (33 weeks), birth weight (less than 1500g) and non-administration of vitamin K and Uvesterol<sup>®</sup>. Premature infants transfused compared to those not transfused had a longer duration of hospitalisation ( $p < 0.001$ ) and more complications during hospitalization ( $p < 0.001$ ). The overall mortality rate was 21.13% with a higher rate in the transfused group (12.68% vs. 8.45%) but no significant ( $p = 0.96$ ).

## Conclusion

Anemia of prematurity is a frequent pathology in this setting, with Blood transfusion as main therapy. Administration of vitamin K and Uvesterol<sup>®</sup> should be ensured in this population while advocating for the access to EPO.

## Introduction

The World Health Organization (WHO) defines prematurity as any birth occurring before 37 weeks of gestation (AS) [1]. It is estimated that 15 million premature births occur each year worldwide, resulting in nearly one million deaths due to complications of prematurity [2]. Globally, prematurity are the leading cause of death in newborns and the second leading cause of death after pneumonia in children under five years of age [3].

In 2010, according to global estimates, more than 60% of preterm births occur in sub-Saharan Africa and South Asia, considered the world's largest birth basins, with significant regional fluctuations [3]. In Cameroon, studies show considerable variability in prematurity rates [2,4,5,6].

Prematurity, a real public health problem is associated to anatomical and physiological immaturity, which exposes the premature to many problems, including anaemia [7].

Anemia in general is defined as a decrease in the overall amount of circulating hemoglobin (Hb), and more specifically, it corresponds to an Hb level less than - 2 standard deviations (SD) from the average for age [8]. All newborns experience a decrease in Hb levels known as "physiological anemia". This decrease varies between 9.5 and 11 g/dl around 10 - 12 weeks in the full-term newborn. On the other hand, premature infants experience a deeper and earlier anaemia called " anaemia of prematurity"[9]. This anemia occurs despite the absence of any pathological cause [10] but diminished plasma erythropoietin level and leads to clinical signs that require management [11].

In view of the global trends in recent years, which indicate an increase in premature births [12], exposing the premature infant to the problem of anaemia, and the scarcity of studies on the subject in our country, it seems important to study the epidemiological, therapeutic and prognostic aspects of premature infant anaemia with a view to contributing to improving the quality of their care and survival.

## **Methodology**

### **1. Type of Study**

We conducted a retrospective cohort study.

### **2. Location of Study**

Our study was carried out in the neonatology unit of the Essos Hospital Centre (CHE) in Yaoundé. CHE is a parapublic hospital structure classified as level II of the health pyramid, housing several specialised services including the neonatology unit. The neonatology unit had human resources (a doctor (head of the unit), a senior nurse and collaborators, and the following equipment (7 closed incubators, 2 radiant heaters, 8 cradles, 2 phototherapy tunnels).

### **3. Care Protocol**

All newborns were subjected to the following systematic biological screening at admission and thereafter: complete blood count and blood group antigens, glucose and calcium levels, C- Reactive Protein (CRP), and any additional specific tests when required..

### **4. Duration and Study population**

From all records of premature newborns hospitalized in the Neonatology Unit from 1 January 2016 to 31 December 2017, we included newborns born before 37 weeks of amenorrhea (AS)witha hemoglobin (Hb)

level of less than 14 g/dl [13] at any time during his stay.

Exclusion criteria:

All files with the following pathologies were found:

- Placenta previahaemorrhagic/ placenta abruption;
- Blood incompatibility (maternal and fetal blood grouping was performed);
- Haemorrhagic

During population follow-up, depending on whether the premature baby was transfused or not, we divided the population into two groups: group A transfusion recipients and group B non-transfusion recipients in order to identify predictive factors for blood transfusion and compare their short-term prognosis.

## 6. Samples

We conducted a consecutive and non-probability sampling.

Definitions of operational terms:

- Prematurity stage:
  - Slight prematurity 34-36 SA ;
  - Moderate prematurity 32-33 SA ;
  - Significant prematurity 28-31 SA ;
  - Extreme prematurity less than 28 SA.
- Severity of anaemia:
  - Mild anaemia: 10-14g/dl ;
  - Moderate anaemia : 7-10g/dl ;
  - Severe anaemia :less than 7g/dl.

## 7. Data entry and statistical analysis

Data were entered and analyzed in Epi Data version 3.1 and R version 3.5.0 software respectively. Statistical analyses of abstracted data were performed using the R software version 3.5.0;; Fisher's exact test which or Chi Square tests were used for assessing association between qualitative variables whenever appropriate; the non-parametric Kruskal-Wallis test (for normal assumption) or ANOVA (alternatively) was used to test the association between qualitative and quantitative variables. A p value below 0.05 was considered significant for all analysis.

# Results

## Prevalence

During the period from January 1, 2016 to December 31, 2017, we consulted 586 cases of premature babies, 153 cases were those of premature babies with a hemoglobin level below 14g/dl at one time during their admission. Of these, 11 files were excluded, including 10 placenta previa files and 1 placenta abruptio file. We definitively included 142 cases of anaemic premature infants for a prevalence of 24.2% of premature anemia.

### **Incidence of blood transfusion**

The three methods used to treat anemia were blood transfusion, iron and EPO. The main use was blood transfusion with an incidence of 57.75%, followed by iron (56.34%) and very few children had received EPO (4.93%).

### **Characteristics of population of blood transfusion**

Depending on whether or not the premature baby was transfused, we divided the population into two groups: a group A of transfused premature babies and a group B of non-transfused premature babies, which allowed us to have the following characteristics (See Table I):

- The majority of the transfused group belonged to the very premature age group (35; 24.65%) with an average gestational age of 30.69 +/- 2.55 AS. The non-transfused group was more likely to be mildly premature (28; 19.72%) with an average gestational age of 32.78 +/- 2.71 AS.
- The median weight in the transfused group was significantly lower (1400[1200-1650]) than in the non-transfused group (1900[1500-2300]).
- -There were no significant gender differences in the two groups.

### **Predictors of blood transfusion**

The gestational age of less than 28 years increased the risk of receiving a blood transfusion by 10 times, an age between 28 and 33 years increased this risk by 6 times. From 34SA onwards, the risk was no longer present in multivariate analysis; the risk of receiving a blood transfusion decreased as gestational age increased.

A birth weight of less than 1500g increased the risk of receiving a blood transfusion by about 8 times; however, a birth weight of 1500g or more protected a premature baby from receiving a blood transfusion by 0.34 times.

Not giving Uvesterol® increased the risk of receiving a blood transfusion by about 6 times.

Not injecting vitamin K increased the risk of receiving a blood transfusion by three times. (See Table II).

### **Immediate outcomes**

Admission duration was significantly longer in the transfused group compared to the non-transfused group (31[18-48] days vs. 7[4.5-18] days). The median exit weight was significantly lower in the

transfused group compared to the non-transfused group (1770[1365-2200] vs. 2150[1700-2650]). More complications were observed in the transfused group compared to the non-transfused group (28.87% vs. 8.45%). There was no significant difference between death and transfusion. The mortality rate was 21.13%; it was higher in the transfused group (12.68% vs. 8.45%). (See Table III).

## Discussion

The prevalence of premature anemia in our study was 24.2%. This result is similar to those obtained by Dick-Amon et al. in 2014 in Côte d'Ivoire and Njom Nlend et al. in 2014 at Yaoundé CHE, which were 25 and 22% respectively[14.2]; however, it was significantly higher than that obtained by Abdelali et al. in 2014 in Morocco which was 3.78%[10]. This could be explained by the consideration of their anemia threshold which was lower than 13g/dl unlike our study where the threshold was lower than 14g/dl.

Anemia of the premature infant was managed at CHE by blood transfusion, oral iron and with the introduction of parenteral EPO. These therapeutic methods were similar to those used by Hays et al. in 2001 in France[15] with the only difference that in their study iron was given by parenteral route and continued orally as soon as parenteral nutrition was stopped.

Blood transfusion was the most commonly used method in our study with an incidence of 57.75%. This result is close to the result obtained by Zhang et al. in 2014 in China, which was 59.3%[16].

However, our result differs from that obtained by Hays et al. in 2001 in France, which was 28%[15]. This could be explained by the fact that in their study, all anemic premature infants received recombinant human erythropoietin (r-hu EPO) subcutaneously 3 times a week from the 5th or 7th day of life, unlike to our study where EPO was given only to 7 premature infants because of a refusal of blood transfusion and a financial problem.

Premature infants transfused were of gestational age and lower birth weight than non-transfused premature infants. This profile is similar to the one obtained by Barthelemy et al. in 2014 in France[17]. This could be explained by the fact that premature transfusion recipients have lower blood mass and EPO production.

In addition, these same factors were the main predictors of blood transfusion. These results corroborate those obtained by Elguazzar et al. in 2013 in Morocco, which also found a role played by the pathologies developed by premature babies, the rate of hemoglobin and hematocrit at birth[18].

Finally, no administration of vitamin K and Uvesterol® was found as predictive factors for blood transfusion. Concerning vitamin K, a factor essential for the synthesis of several coagulation factors, its absence would lead to a decrease in these factors and a hemorrhagic risk would become possible, which would require blood transfusions. As for Uvestérol® (a vitamin complex containing vitamins A, D, E and C), its protective role through vitamin E is known contained in the product as an antioxidant, protecting red blood cells from peroxidation and membrane damage. Its absence would lead to the destruction of

red blood cells and a lack of heme synthesis, which would contribute to a decrease in hemoglobin and the use of blood transfusions[8]. In our study, EPO did not play a role in protecting the risk of receiving a blood transfusion, this could be explained by the very small sample of patients that received this molecule.

Admission duration was longer in the transfused group, a similar result with Jeon et al. in 2013 in Korea[9]. Complications during were more frequent in the transfused group, a result parallel to that of Banerje et al. in 2015 in England[19]. The overall mortality rate was 21.13% with a higher rate in the transfused group (12.68% vs. 8.45%) but not significant. This result is similar to those obtained by Hasenbegovic et al. in 2010 in Bosnia[20] and Dick-Amon et al. in 2014 in Côte d'Ivoire[14], which found 21% and 26% of the mortality rate respectively.

## **Conclusion**

The results obtained indicate that the prevalence of premature anemia is still high, and the vast majority of premature infants are managed by blood transfusion in our context. The complications associated with the use of this practice allow us to focus on preventing premature anemia through the use of EPO as well as certain techniques such as delayed cord clamping and reduced phlebotomy.

## **Declarations**

### **Ethical approval and consent to participate**

This work was approved by the Institutional Ethics Committee of the Essos Hospital Centre of Yaoundé by ethical clearance No. 2018/06/CE-CHE and the Institutional Ethics Committee of the University of Douala No. 1445CEI-Udo/04/2018/T. An administrative authorization was given by the directorate of hospital to access to files and registers. Data were processed using unique identifiers for purpose of privacy and confidentiality

### **Availability of data and material**

Data underlying these findings are provided in the manuscript tables and figures. Complete dataset could be provided upon reasonable request from the corresponding author. This dataset represents a core of the hospital database and may not be deposited in a public repository.

### **Competing interests**

The authors declare that they have no competing interests

### **Funding**

No funding was allocated for this study

## Contributions of Authors

- LA: conceptualization, protocol writing, data collection, final manuscript writing.
- ABS: data analysis.
- POKN: supervision, proofreading of the final manuscript, validation
- AENN: follow-up of the methodology, editing of the manuscript, proofreading of the final manuscript, validation.

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## Tables

**Table 1** :Preterm birth features and blood transfusion.

<b>IVariables</b>	<b>Transfusion n= 82 57,75%</b>	<b>No transfusion n= 60 42,25%</b>	<b>p-value</b>
<b>Gestationalage (SA)</b>	Mean +/- standard deviati		<b>&lt; 0,0001</b>
< 28	30,69 +/- 2,55 8 (5,63)	32,78 +/- 2,71 2 (1,41)	
28-31	35 (24,65)	15 (10,56)	
32-33	29 (20,42)	15 (10,56)	
34-37[	10 (7,04)	28 (19,72)	
<b>Birthweight (g)</b>	Mediane[Q1-Q3]		<b>&lt; 0,0001</b>
< 1500	1400 [1200-1650] 48 (33,81)	1900[1500-2300] 14 (9,86)	
≥1500	34 (23,94)	46 (32,39)	
<b>Gender</b>			0,31
Male	39 (27,47)	23 (16,20)	
Female	43 (30,28)	37 (26,05)	

**Table II** :Predictive factors of blood transfusion.

	Unadjusted Odd Ratio (95% CI)	Adjusted Odd ratio (95% CI)
<b>Gestationalage</b>		
< 28	11,20 (2,34-83,18)	10,13 (2,03-77,18)
28-31	6,53 (2,62-17,44)	6,27 (2,41-17,57)
32-33	5,41 (2,14-14,60)	6,16 (2,34-17,44)
34-37[	ref	ref
<b>Birthweight</b>		
< 1500	8,17 (2,43-18,65)	7,75 (2,38-15,90)
≥ 1500	0,22 (0,10-0,44)	0,34 (0,11-0,88)
<b>Gender</b>		
male	1,46 (0,74-2,89)	1,36 (0,63-2,96)
female	ref	ref
<b>Uvestérol®</b>		
No	8,14 (3,78-18,75)	5,58 (2,33-14,22)
yes	ref	ref
<b>Vitamine K</b>		
No	2,16 (1,09-4,38)	3,00 (1,29-7,37)
Yes	ref	ref
<b>EPO</b>		
Yes	1,88 (0,39-13,47)	1,40 (0,27-10,47)
No	ref	ref

CI:ConfidenceInterval

**Table III** :Outcomes of anemia in preterm new born babies according to blood transfusion stratus

	<b>Population (N=142 ; 100%)</b>	<b>Transfused (n=82 57,75%)</b>	<b>Not transfused (n=60 42,25%)</b>	<b>p- value</b>
<b>Legnth of stay in days (Mediane[Q1-Q3])</b>	20,25 [7-35]	31 [18-48]	7 [4,5-18]	<b>&lt; 0,001</b>
<b>Weight at discharge in g (Mediane[Q1-Q3])</b>	1960 [1500-2400]	1770 [1365- 2200]	2150 [1700-2650]	<b>0,024</b>
<b>Adverse events during hospitalization n(%)</b>				<b>&lt; 0,001</b>
Yes	53 (37,32)	41 (28,87)	12 (8,45)	
No	89 (62,68)	41 (28,87)	48 (33,80)	
<b>Deaths n(%)</b>				<b>0,96</b>
Yes	30 (21,13)	18 (12,68)	12 (8,45)	
No	112 (78,87)	64 (45,07)	48 (33,80)	