Evaluation of Neonatal Polycythemia in Terms of Gestational Age, Hematocrit, and Platelet Levels

Yenidoğan Polisitemisinin Gebelik Yaşı, Hematokrit ve Trombosit Düzeyleri Açısından Değerlendirilmesi

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ABSTRACT

Objective: The main concern in neonatal polycythemia is complication development due to hyperviscosity. We aimed to compare symptoms, clinical and laboratory features, and organ dysfunctions of polycythemic newborns with respect to gestational age, hematocrit (hct) levels and presence of thrombocytopenia.

Material and Methods: Between January 2013 and December 2016, all hospitalized newborns with a gestational age of ≥ 34 weeks were retrospectively evaluated and those with a venous hct value exceeding 65% were included. Exclusion criteria were infections, metabolic diseases and congenital anomalies. Newborns were grouped and compared according to hct values (65–69.9% vs. ≥70%), gestational age (late preterm vs. term) and thrombocytopenia (present/absent).

Results: Polycythemia incidence was 7.7% in the study group. The most common symptoms were hypoglycemia and hyperbilirubinemia, while 35.1% of newborns were asymptomatic. Hypoglycemia, hypocalcemia, and plethora were significantly more frequent in the severe polycythemia (hct ≥70%) group than in the moderate polycythemia (hct between 65–69.9%) group ($p = 0.027$, $p = 0.014$, $p < 0.001$, respectively). Hyperbilirubinemia was more common in late preterm babies than term babies ($p = 0.014$). Feeding difficulty, convulsion, hypoglycemia, hypocalcemia and liver function test abnormalities were significantly more common in newborns with thrombocytopenia than those without ($p = 0.002$, $p = 0.004$, $p < 0.001$, $p = 0.022$, $p = 0.043$, respectively).

Conclusion: It should be kept in mind that more than one-third of polycythemic newborns may be asymptomatic. While the most common symptoms were hypoglycemia and hyperbilirubinemia, liver function tests may also be adversely affected.

Key Words: Hematocrit, Hyperviscosity, Late preterm, Newborn, Thrombocytopenia

ÖZ

Amaç: Yenidoğan polisitemisinde esas sorun hiperviskoziteye bağlı komplikasyonlardır. Bu çalışmanın amacı polisitemik yenidoğanların semptomlarını, klinik ve laboratuvar özelliklerini ve organ işlev bozukluklarını; gestasyonel yaş, hematokrit (hct) düzeyleri ve trombositopeni varlığı açısından değerlendirmektir.

Gereç ve Yöntemler: Ocak 2013 ile Aralık 2016 tarihleri arasında, hastanede yatan gestasyonel yaşı≥34 hafta olan tüm yenidoğanlar geriye dönük olarak değerlendirildi. Venöz hct değerleri %65'in üzerinde olan yenidoğanlar çalışmaya dahil edildi. Enfeksiyon, metabolik hastalık ve konjenital anomalileri olan yenidoğanlar çalışma dışı bırakıldı. Yenidoğanlar hct değerlerine (Orta derece polisitemi [%65-69] ve Şiddetli derece polisitemi [≥%70]), gestasyonel yaşa göre (geç preterm/term) ve trombositopeni durumuna (var/yok) göre gruplandırıldı ve karşılaştırıldı.

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Contribution of the Authors / Yazarların katkısı*: *YALCINKAYA R: Constructing the hypothesis or idea of research and/or article, Planning methodology to reach the Conclusions, Taking responsibility in patient follow-up, collection of relevant biological materials, data management and reporting, execution of the experiments, Taking responsibility in logical interpretation and conclusion of the results, Taking responsibility in necessary literature review for the study, Taking responsibility in the writing of the whole or important parts of the study. ***ZENCIROGLU A:*** Constructing the hypothesis or idea of research and/or article, Planning methodology to reach the Conclusions, Organizing, supervising the course of progress and taking the responsibility of the research/study, Taking responsibility in patient follow-up, collection of relevant biological materials, data management and reporting, execution of the experiments, Taking responsibility in the writing of the whole or important parts of the study, Reviewing the article before submission scientifically besides spelling and grammar.

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Bulgular: Çalışma grubunda polisitemi insidansı %7.7 olarak saptandı. En sık görülen semptomlar hipoglisemi ve hiperbilirubinemi iken, yenidoğanların %35.1'i asemptomatikti. Hipoglisemi, hipokalsemi ve pletore şiddetli polisitemi grubunda orta polisitemi grubuna göre anlamlı olarak daha sıktı (sırasıyla p= 0.027, p= 0.014, p< 0.001). Hiperbilirubinemi, geç preterm bebeklerde term olanlara göre daha sıktı (p= 0.014). Trombositopenisi olan yenidoğanlarda, beslenme güçlüğü, konvülziyon, hipoglisemi, karaciğer fonksiyon testleri anormallikleri, trombositopenik olmayanlara göre anlamlı olarak daha fazlaydı (sırasıyla p= 0.002, p = 0.004, p < 0.001, p = 0.022, p = 0.043).

Sonuç: Polisitemik yenidoğanların asemptomatik olabileceği akılda tutulmalıdır. En sık görülen semptomlar hipoglisemi ve hiperbilirubinemi iken, karaciğer onksiyon testleri de polisitemik yenidoğanlarda etkilenebilir.

Anahtar Sözcükler: Hematokrit, Hiperviskozite, Geç preterm, Yenidoğan, Trombositopeni

INTRODUCTION

Neonatal polycythemia, defined as a venous hematocrit (hct) value higher or equal to 65% at birth, is associated with blood hyperviscosity. As the viscosity increases, there is often progressive impairment of tissue oxygenation and perfusion, possibly causing significant damage. Although symptoms of hypoperfusion correlate better with blood viscosity as compared to hct value, viscosity is difficult to measure. Since instruments to measure viscosity are not available in most neonatal intensive care units, hyperviscosity is usually suspected in the presence of suggestive symptoms and/or an abnormally high hct values. The frequency of neonatal polycythemia is reportedly between 0.4–12%, but results are significantly affected by many confounding factors, including but not limited to gestational characteristics, maternal health, altitude, and the efficiency and swiftness of cord clamping after delivery (1,2).

Significant damage may occur in polycythemia due to impairment of tissue oxygenation and perfusion (3). To our knowledge, the number of studies which have evaluated neonatal polycythemia according to gestational age, hct levels, platelet levels (all together) are very limited. Therefore, this study was planned to determine the frequency and symptomatology of polycythemia in newborns, and also to compare the symptoms, clinical and laboratory findings of polycythemic newborns in terms of gestational age, hct groups, and presence/absence of thrombocytopenia.

MATERIALS and METHODS

This study was a retrospective evaluation of neonates who were hospitalized in a single tertiary neonatal intensive care unit between January 2013 and December 2016. Newborn babies with a gestational age of ≥34 weeks who had an hct value of 65% or higher in venous blood samples drawn at >4 hours of age were included. Exclusion criteria were infections, metabolic diseases and congenital anomalies.

Newborns were grouped and compared according to hct values (moderate polycythemia (65%- 69%) vs. severe polycythemia (≥70%)), gestational age (late preterm vs. term) and thrombocytopenia (present/absent). Gestational age groups of the babies were defined as late preterm ($34^{0/7}$–$36^{6/7}$weeks) and term ($37^{0/7}$–$41^{6/7}$ weeks). The gestational development of neonates was assessed according to Lubchenco's intrauterine growth curves (4). Small for gestational age (SGA) and large for gestational age (LGA) were defined as birth weight less than the 10^{th} percentile and higher than the 90^{th} percentile for gestational age, respectively. Neonates with a weight between the 10^{th} and 90^{th} percentiles were defined as appropriate for gestational age (AGA) (5). Hyperbilirubinemia was defined as bilirubin level which warranted phototherapy (6). Hypoglycemia was defined as a serum glucose level of <40 mg/dL, hypocalcemia was defined as a serum calcium level of <7.6 mg/dl, and thrombocytopenia was defined as a serum platelet level of $<150.000/mm^3$ (7). If the aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT) levels were not within the reference range adjusted for age and sex, newborns were defined to have abnormal liver function test (LFT) (7). Creatinine elevation was defined as the detection of serum creatinine levels exceeding 1.3 mg/dl (8). Apnea was defined as cessation of breathing for more than 20 seconds, tachypnea was defined as respiratory rate greater than 60 breaths per minute. If the above findings (including apnea and convulsions) were caused by only polycythemia and other reasons were not present (such as hypoglycemia and hypocalcemia), the findings were recorded.

Newborns' sex, postnatal age (in hours) at polycythemia diagnosis, prenatal and natal history, recorded risk factors (in terms of SGA, fetal distress history, LGA, gestational diabetes, preeclampsia, maternal hypertension), type of birth, hct values at diagnosis, symptoms and findings associated with polycythemia (feeding difficulty, plethora, tachypnea, apnea, convulsion, cyanosis), treatment, and laboratory results consisting of complete blood count, creatinine, ALT, AST and C-reactive protein were recorded from the institutional electronic database. Laboratory tests were only performed in the presence of suspicion or risk factors for polycythemia. All newborn babies were evaluated by an attending neonatologist.

During the study period, the treatment approach of our neonatology clinic for polycythemic babies was as follows: Partial exchange transfusion (PET) was performed in those with a hct level in excess of 75% regardless of the presence or absence of symptoms. In those with hct levels between 65-74%, after evaluation for other possible causes, treatment was applied in two groups according to the symptoms. Asymptomatic newborns with hct values lower than 70% were monitored with oral feeding, whereas those with hct greater

than 70% received one of the following: close monitoring and intravenous (IV) hydration, or PET. The decision for treatment approach was based on the opinion of the attending physician. Local ethical approval was obtained from the committee of our institution (E-73799008-799).

Statistical Analysis

All statistical analyses were performed with SPSS (version 21) computer software (SPSS Inc., Chicago, IL, USA). Quantitative variables were given as mean ± SD and qualitative variables were given as frequency and percentage. The normality of distribution of quantitative variables was assessed via the Kolmogorov-Smirnov with Lilliefors correction. The comparison of groups based on hct levels (moderate/severe polycythemia), gestational age (late preterm/term) and thrombocytopenia (presence/absence) were performed with the Student's t-test (normal distribution) and the Mann Whitney-U test (non-normal distribution). The correlations between quantitative variables were checked by the calculation of Pearson and Spearman correlation coefficients depending on normality of distribution. Categorical comparisons were performed via Chi-squared tests. P-values lower or equal to 0.05 were considered to demonstrate statistical significance.

RESULTS

There were a total of 4497 hospitalized newborns with a gestational age ≥ 34 weeks during the study period. Among these, 421 newborns had a hct value of ≥ 65% in samples obtained at > 4 hours of age. Seventy-four newborns were excluded according to exclusion criteria. Thus, a final group of 347 neonates (189 (54.5%) males) were included in the analyses (Figure 1).

The frequency of neonatal polycythemia was 7.7% in our study group. Thirty-five percent of the babies (n= 122) were asymptomatic. The most common symptoms, in order of frequency, were as follows: hypoglycemia (32.5%), feeding difficulty (11.8%), tachypnea (6.9%), plethora (5.4%), cyanosis (5.1%), convulsion (2.8%), and apnea (1.1%) (Table I).

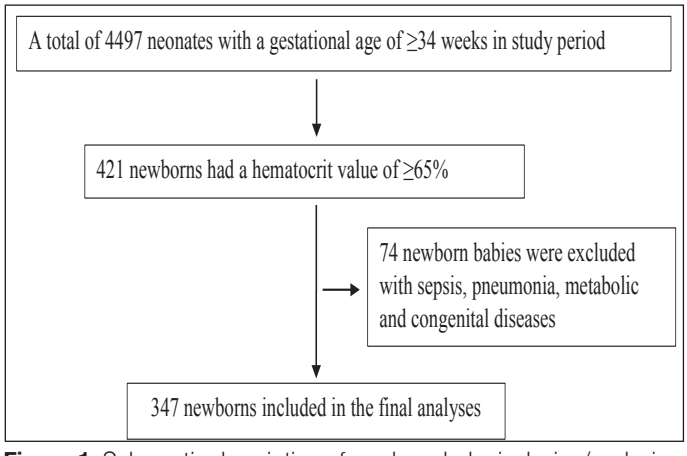

Figure 1: Schematic description of newborn baby inclusion/exclusion.

Table I: Demographic, clinical and laboratory data of all polycythemic newborn babies.

	Polycythemic newborns (n=347)
Gender, boys, n(%)	189 (54.4)
C/S, n(%)	232 (66.8)
Gestational age, weeks	38 ± 1.5
Birth weight, gram	2954 ± 681
Mother age, years	28.6 ± 6.3
SGA, n(%)	111 (31.9)
Late preterm, n(%)	60 (17.2)
Gestational diabetes, n(%)	22 (6.3)
Asymptomatic, n(%)	122 (35.1)
Symptoms, physical examination findings and laboratory results	
Feeding difficulties	41 (11.8)
Plethora	19 (5.4)
Tachypnea	24 (6.9)
Apnea	4 (1.1)
Convulsion	10 (2.8)
Cyanosis	18 (5.1)
Hypoglycemia	113 (32.5)
Hyperbilirubinemia	103 (29.6)
Thrombocytopenia	78 (22.4)
Hypocalcemia	15 (4.3)
Elevation of creatinine levels	10 (2.8)
LFT abnormality	9 (2.5)
Aspartate aminotransferase* (U/L)	309.4 ± 231.98
Alanine aminotransferase* (U/L)	127.5 ± 97.3
Treatment	
Observation	192 (55.3)
IV hydration	83 (23.9)
PET	72 (20.7)

mean ± SD, **C/S: Caesarian section, **IV:** Intravenous, **LFT:** Liver function tests, **PET:** partial exchange transfusion, **SGA:** Small for gestational age.*

With regard to risk factors, 111 (32%) of polycythemic newborns were SGA, 35 (10%) had fetal distress history, 32 (9.2%) were LGA, 26 (7.4%) had maternal gestational diabetes, and 11 (3.1%) mothers had preeclampsia or maternal hypertension.

When newborns were compared with regard to polycythemia severity (moderate vs. severe), the frequencies of any type of symptom, hypoglycemia, hypocalcemia and plethora were significantly higher in those with severe polycythemia (p= 0.028, p= 0.027, p= 0.014 and p< 0.001, respectively) (Table II).

Comparisons based on gestational age demonstrated that the frequency of hyperbilirubinemia was significantly higher in late-preterm newborns than term newborns (41.6% vs 27.1%, respectively; p= 0.014) (Table III).

When polycythemic newborns were compared with regard to presence of thrombocytopenia, thrombocytopenic ones

Table II: Comparison of polycythemic newborns in terms of hematocrit levels.

	Moderate polycythemia (n=273)	Severe polycythemia (n=74)	p
Asymptomatic, n,%	104 (38)	18 (24.3)	**0.028**
Symptoms, physical examination findings, laboratory results %			
Feeding difficulties	34 (12.4)	7 (9.4)	0.487
Plethora	8 (2.9)	11 (14.8)	**<0.001**
Tachypnea	20 (7.3)	4 (5.4)	0.564
Apnea	3 (1)	1 (1.3)	0.857
Convulsion	6 (2.1)	4 (5.4)	0.143
Cyanosis	12 (4.3)	6 (8.1)	0.194
Hypoglycemia	81 (29.6)	32 (43.2)	**0.027**
Hyperbilirubinemia	83 (30.4)	20 (27)	0.675
Thrombocytopenia	55 (20.1)	23 (31)	**0.046**
Hypocalcemia	8 (2.9)	7 (9.4)	**0.014**
Elevation of creatinine levels	6 (2.1)	4 (5.4)	0.153
LFT abnormality	7 (2.5)	2 (2.7)	0.957

LFT: *Liver function tests.*

Table III: Comparison of polycythemic newborns in terms of gestational age.

	Late preterm babies (n=60)	Term babies (n=287)	p
Asymptomatic, n,%	15 (25)	107 (37.2)	**0.070**
Symptoms, physical examination findings and laboratory results %			
Feeding difficulties	8 (13.3)	33 (11.4)	0.622
Plethora	5 (8.3)	14 (4.8)	0.285
Tachypnea	4 (6.6)	20 (6.9)	0.933
Apnea	1 (1.6)	3 (1)	0.682
Convulsion	0	10 (3.4)	0.142
Cyanosis	5 (8.3)	13 (4.5)	0.232
Hypoglycemia	25 (41.6)	88 (30.6)	0.098
Hyperbilirubinemia	25 (41.6)	78 (27.1)	**0.014**
Thrombocytopenia	13 (21.6)	65 (22.6)	0.868
Hypocalcemia	1 (1.6)	14 (4.8)	0.266
Elevation of creatinine levels	1 (1.6)	9 (3.1)	0.512
LFT abnormality	1 (1.6)	8 (2.7)	0.565

LFT: *Liver function tests*

Table IV: Comparison of polycythemic newborns in terms of thrombocytopenia.

	Thrombocytopenic newborns (n=78)	Non- thrombocytopenic newborns (n=269)	p
Asymptomatic, n,%	11 (14.1)	111 (41.2)	**<0.001**
Symptoms, physical examination findings and laboratory results %			
Feeding difficulties	16 (20.5)	25 (9.2)	**0.002**
Plethora	6 (7.6)	13 (4.8)	0.328
Tachypnea	9 (11.5)	15 (5.5)	0.068
Apnea	2 (2.5)	2 (0.7)	0.185
Convulsion	6 (7.6)	4 (1.4)	**0.004**
Cyanosis	7 (8.9)	11 (4)	0.076
Hypoglycemia	39 (50)	74 (27.5)	**<0.001**
Hyperbilirubinemia	26 (33.3)	77 (28.6)	0.219
Hypocalcemia	7 (8.9)	8 (2.6)	**0.022**
Elevation of creatinine levels	6 (7.6)	4 (1.4)	0.289
LFT abnormality	5 (6.4)	4 (1.4)	**0.043**

LFT: *Liver function tests.*

more frequently suffered from feeding difficulty, convulsion, hypoglycemia, hypocalcemia, and LFT abnormality compared to those without (p= 0.002, p= 0.004, p< 0.001, p= 0.022, p=0.043, respectively) (Table IV).

DISCUSSION

In the literature, the frequency of neonatal polycythemia is reported in a wide range between 0.4% and 12% (1). In the current study, we found a frequency of 7.7% in newborns with a gestational age of ≥ 34 weeks at our center. This value is in agreement with previous studies and also shows that newborn polycythemia is an important problem.

SGA is one of the known risk factors for neonatal polycythemia. In our study group, SGA was present in 32% of our patients. The literature on this topic reports ranging from 24.7% to 55.5% (9-11). Although data is limited on this topic, it is possible that these variations are caused by population-based characteristics. Polycythemia has also been associated with LGA, but the results of the few studies vary greatly, with reports ranging from a frequency of 4% to 20% (12,13). In our group, 9.2% of newborns were defined to be LGA. Because gestational characteristics are directly associated with maternal health and care during pregnancy, standardizing obstetric care and increasing physicians' awareness of this condition may benefit patients and clinicians alike.

Our evaluation revealed that 64.9% of our newborns were symptomatic. This frequency was compatible with literature in which percentages have been reported from 60% to 90% (14, 13). In this study, hypoglycemia and feeding difficulties were found to be the most frequent symptoms, representing almost 45% of the whole group. In two prospective studies, the most frequent symptoms of neonatal polycythemia were reported to be gastrointestinal symptoms (vomiting and feeding difficulties) in 17%, hypoglycemia in 12%, and cyanosis/apnea in 10% (15,16). We found that hyperbilirubinemia was present in 29.6% of our study group, which is in compatible with previous studies (29%, 46.5% and 33%) (17,11,13). Neurological symptoms, which are among the most feared consequences of polycythemia, were rare in this study. Only 10 newborns (2.8%) had convulsions, and no other problems were reported. A convulsion rate of 28% was reported in a study comprised of 18 newborns; whereas, no such events were reported in studies including 54 and 111 newborns, respectively (19, 16,18,19). Paucity of neurological findings in our study and also the latter studies may have been associated with the fact that newborn convulsions are often subtle and difficult to recognize which may lead to underestimation of frequency (20). Plethora was seen in only 14.9% of the babies with hct levels above 70% demonstrating that plethora is indeed an unreliable finding for polycythemia.

It is well-known that newborns with polycythemia have a significantly increased likelihood for developing symptoms such as hypoglycemia, hypocalcemia, hyperbilirubinemia and neurological problems (21). In this study, newborns with severe polycythemia were more likely to have any symptom related to polycythemia. Also, hypocalcemia, hypoglycemia, and plethora were more common in severe polycythemia group compared to moderate polycythemia. Level of 70% seems to be a threshold at which circulatory resistance shows dramatic increase (22). There is no consensus yet on which hct value requires treatment. Supportive treatment is generally recommended for asymptomatic patients above 65%, and partial blood exchange transfusion is recommended for symptomatic patients (23). Our findings emphasize that in newborns with hct above 65%, the signs and symptoms should be sought carefully, considering that the symptoms may be subtle in newborns.

Polycythemic newborns were also evaluated in terms of gestational age in this study. Although polycythemia is usually a problem in the post-term population, recent studies have revealed that early term and late preterm birth may also pose risks for polycythemia (24). The percentage of symptomatic newborns was not found to be significantly different in late preterm infants compared to term infants in our study but the frequency of hyperbilirubinemia was more frequent in the late preterm group. To our knowledge, there is currently no study that can provide comparative data of polycythemic term and preterm babies, however there is a study with 6402 babies -of which 681 were late preterm and 5721 were term- the authors aimed to compare morbidity and mortality between late preterm and term infants and provided an extensive dataset. Their findings demonstrated that hyperbilirubinemia was more common in late preterm babies than term ones (24). Although preterm babies are often thought to be predisposed to anemia because they do not go through the last trimester, our findings emphasize that physicians should be aware that polycythemia may also be seen in this group. However, it is difficult to differentiate whether the problems are associated with prematurity or polycythemia itself; thus, in order to be able to differentiate prematurity and polycythemia symptoms, all late preterm babies should be assessed carefully.

Thrombocytopenia is an expected finding in polycythemia. We found that thrombocytopenia was present in 22.4% of our patients. The literature on this topic shows a remarkably wide range; from 5% to 51% (25-27). It is known that patients with thrombocytopenia have increased risk for respiratory distress, apnea and convulsions and worse laboratory values including bilirubin and leukocyte levels (25,27). Similarly, we found that feeding difficulties, hypoglycemia, hypocalcemia, convulsions, and abnormalities in LFT were significantly more frequent in patients with thrombocytopenia. In a study which evaluated thrombocytopenia in 140 polycythemic newborns, hyperbilirubinemia was more common in babies with low plt levels (27). These results demonstrate the extreme importance

of monitoring platelet levels in patients with polycythemia in order to prevent morbidity and mortality.

The strengths of this study include the high number of newborns and the presence of detailed medical history. To our knowledge, this is the first study to include a newborn group of this size, and to perform evaluations based on hct levels, gestational age, and presence of thrombocytopenia. However, there are also limitations to be discussed. Firstly, this is a retrospective study and carries all limitations associated with this design even though we applied strict inclusion/exclusion criteria. Secondly, data records may not have been accurate in some instances (especially in antenatal history) and it is also possible that there were important differences among each physician with regard to their clinical notes. Lastly, the lack of long-term follow-up, especially for neurological problems, is an important limitation.

As conclusion, the analysis of our data indicates that polycythemia is a frequent problem in our newborn population. While two-thirds of newborns were symptomatic, one-third did not show any symptoms at all, indicating the importance of assessing risk factors and ordering blood tests accordingly. In this study, we demonstrated differences between groups formed on the basis of hct levels, gestational age and the presence of thrombocytopenia. Prospective studies are needed to determine the actual effects of polycythemia and its relationship with symptomatology.

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