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Evaluation of the incidence and risk factors of neonatal polycythemia

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Abstract
Aim: We aimed to evaluate the hematocrit levels of neonatal polycythemia patients with time relation and to understand their relationship with the treatment method, so that neonatal polycythemia can be better understood.
Material and Methods: We conducted a retrospective study in newborn polisitemi patients with data in NICU over a 1-year-period (december 2013-december 2014). The relationship between the treatment modalities applied to patients hospitalized with the diagnosis of polycythemia and the 1st hour, 12th hour and 24th hour hematocrit levels were examined.
Results: This study was carried out on a total of 50 infants hospitalized in our unit with the diagnosis of polycythemia. Partial exchange therapy (PET) therapy was evaluated as fluid therapy and observation therapy groups. 1st hour, 12th hour and 24th hour hematocrit levels were calculated for each of them separately.
Discussion: When the relationship between hematocrit values and treatments was examined, it was observed that those who received fluid therapy had lower hospitalization (1 hour) Hct values than those who did not receive fluid therapy. In contrast to partial exchange transfusion, restrictive management has been confronted with several difficulties. It is therefore imperative to conduct more thorough large-scale cohort studies to further understand the reasons for this.

Keywords
Newborn, Polycythemia, Hematocrit, Treatment

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Introduction

An increase in erythrocyte mass is known as polycythemia. The form seen in adults is called polycythemia vera, while the form seen in newborns is called polycythemia neonatorum. In the newborn period, the most important factor causing hyperviscosity is hematocrit [1-3]. The hematocrit level peaks at 2-4 hours of age and this situation can reflect normal fetal adaptation. After that decreases gradually [6]. Polycythemia neonatorum is defined as either venous hematocrit levels above 65% [4-5].

Hyperviscosity refers to increased resistance to blood fluidity. Especially, increased resistance is related to structure and content of blood. There are a lot of factors in the blood component like leukocytes, platelets, plasma proteins, immunoglobulins and coagulation factors are the other cellular elements which affect the whole blood viscosity [10]. The main cell of blood is Red Blood Cell (RBC) [8]. An increased RBC mass level increases the venous hematocrit level. On the other hand, the factors affecting the viscosity are surface tension and sliding velocity. If the surface tension is considered to be the same for human vascular endothelia, the important factor becomes the sliding velocity in this situation. The sliding velocity is affected by the density of the blood. Consequently, these factors indicate that hyperviscosity is a circulatory disorder [3].

So polycythemia and hyperviscosity have a strong relationship, but they have different definitions [5]. Polycythemia and hyperviscosity are common in the newborn [10]. Pathophysiological mechanism due to the effects of hyperviscosity. Local effects of hyperviscosity: hypoxia, acidosis, hypoglycemia and causing the thrombus in the microcirculation [16].

Its incidence is reported between 1 to 5% [1-5]. However, It has been reported to occur at a rate of 10-15% in small for gestational age (SGA) , in large for gestational age (LGA) babies 6-8%.[1, 11].

Polisytemia have a posibillity to cause some symptoms and complications due to hemodynamic effects of hyperviscosity. Most of the newborns (74-90%) are asymptomatic [5]. Hyperviscosity can cause tissue perfusion disorder and metabolic complications such as hypoglycemia and hypocalcemia. Nonspecific signs and symptoms such as tremor, lethargy, cyanosis, vomiting, respiratory distress, seizures apnea, , feeding problems, irritability and jitteriness may be seen. Most comon symptoms seems due to central nervous system, renal and adrenal system, cardiopulmonary system and gastrointestinal system [16].

In symptomatic newborns, the most common problems are central nervous system disorders. Central nervous system symptoms are letargy, hiperirritability, vomiting, jitteriness, convulsion, hypotonia and seizures. The most common metabolic problems encountered is hypoglycemia (12-40%). Renal problems are oliguria, hematuria, proteinuria and renal vein thrombosis. Cardiopulmonary complications with tachycardia and tachypnea may occur. Thrombocytopenia and thrombosis are hematological problems in polycythemia [5].

Material and Methods

Study Setting

In our study we conducted a retrospective cohort study by screening the records of all neonates who had been admitted to our NICU during the past 12 months, from December 2013 to December 2014. We did our study at Ümraniye Education and Training Hospital, which has around 3500 deliveries per year and an average of 800-900 admissions to NICU per year.

Our study was conducted in accordance with the Declaration of Helsinki. All data used in this study were anonymized before statistical analysis and reporting. Among the patients who were admitted to the NİCU and had the P61.1 code in the ICD coding system, those were selected from the hospital automation system. Their symptoms, laboratory data and outcomes were recorded.

Study Design and Patient Characteristics: This study aimed to investigate neonatal polycythemia, with a focus on patient demographics (gender, gestational age, mode of delivery), risk factors for polycythemia (small for gestational age [SGA], large for gestational age [LGA], birth asphyxia [DAB], low Apgar scores), clinical symptoms (jaundice, tachypnea, poor feeding, vomiting, lethargy, apnea, cyanosis), laboratory abnormalities (hypoglycemia, hypocalcemia, thrombocytopenia), and hematocrit (Hct) values at admission (1st hour), 12 hours, and 24 hours post-admission. Hypoglycemia was defined as a serum glucose level below 47 mg/dL, hypocalcemia as a calcium level below 8 mg/dL, and thrombocytopenia as a platelet count below 150,000/mm^3.

Hyperviscosity Assessment: To diagnose hyperviscosity, measurement of blood viscosity is required, typically using a viscometer. However, for the diagnosis of polycythemia, measurements are based on Hct values. In the neonatal period, the most significant factor contributing to hyperviscosity is Hct. Currently, neonatal polycythemia is defined as a venous Hct of 65% or higher.

Blood Sampling and Hct Measurement: Blood samples from the study participants were collected via venous micro-capillary tubes. Following centrifugation for three minutes using a microcentrifuge, plasma was separated, and the packed cell volume was measured. A diagnosis of neonatal polycythemia was established if venous Hct levels at postnatal 6 hours and beyond were equal to or exceeded 65%.

Management of Polycythemia: Based on the Hct levels, the following management approaches were adopted:

1. For Hct levels between 65-70 with no symptoms, patients were closely monitored.
2. If Hct levels were between 70-75 with no symptoms, intravenous administration of 10cc/kg of 0.9% NaCl solution was performed over one hour.
3. Patients with Hct levels exceeding 75 or within the range of 65-75 with symptoms underwent partial exchange transfusion. The goal of partial exchange transfusion was to reduce hematocrit levels to 55%.

Inclusion and exclusion criteria

Among the patients who were admitted to the NİCU and had the P61.1 code in the ICD coding system, those were selected. Inclusion criteria were: [1] Venous hct ≥65% in the first 7 days of life [2]. Neonates born in our institution [3]. Gestational age ≥34 weeks. Exclusion criteria: [1]. Blood samples taken from the heel were excluded from the study due to the variations and weaknesses of capillary measurement [2]. Neonates who died in the first 7 days of life. In addition, patients with missing data

were also excluded from the study.

Primary Outcome

The primary aim of our study was to evaluate the hematocrit levels of neonatal polycythemia patients with time relation and to understand their relationship with the treatment method, so that neonatal polycythemia can be better understood.

Statistical Analysis

Statistical analysis of the research was done with SPSS 15.0 (Statistical Package for Social Sciences) and GraphPad InStat demo version program. Frequency and descriptive statistics were calculated. In descriptive statistics, continuous variables were presented as median (min-max), and categorical variables as percentages. Chi-square and Fisher-Freeman Halton Test were used to reveal the difference between categorical bivariate groups. We used Kruskal Wallis test for means between three groups, Dunn's test for pairwise comparisons, Friedman test for the comparison of means at three different times, and then Wilcoxon rank test for pairwise comparisons. The study analyzes were made at 95% confidence interval and $p<0.05$ significance level.

Ethical Approval

This retrospective study is derived from the first author's medical specialty thesis. This thesis is also registered in the national thesis center with the reference number 809744.

Results

Polycythemia was found in 50 of the 806 infants who were admitted to the NICU. 30 of them were male (60%) and It was seen that 20 of them were girls (40%). The incidence of polycythemia in our unit was determined as 6.2%

Twenty-four (48%) neonates were born with normal spontaneous delivery (NSD) and 26 (52%) with cesarean (C/S), according to the type of delivery of the babies hospitalized in the NICU with the diagnosis of polycythemia (Figure 1).

Among infants with polycythemia hospitalized in the NICU, it was observed that the lowest birth weight was 1130 g, and the highest was 5350 g. The mean weight was found to be 3015.5 g (ss: ±991.11). When the distribution of polycythemic newborns by the gestational age examined, it was seen that the mean week 37.60±1.95 with the ranges from 32 to 40 weeks. It was observed that 22% of polycythemic infants hospitalized in the NICU were preterm and 78% were term infants (Figure 2).

When the weights of the patients were evaluated to compared with their gestational age, the number of Small for Gestational Age (SGA) infants was 16, Appropriate for Gestational Age (AGA) infants was 19 and the Large for Gestational Age (LGA) infants was 15. So, 32% were SGA and 30% LGA and 38% were followed as AGA babies (Figure 3).

When the 1st and 5th minute APGAR scores of polycythemic newborns were evaluated, we found that the Apgar 1st minute score ranged from 2 to 9 with a mean of 8.08±1.47, and the Apgar 5th minute score ranged from 5 to 10, with a mean of 9.34±1.04.

The most common symptoms were jaundice (40%), hypoglycemia (24%) and poor nutrition (26%); other symptoms were determined as lethargy (22%), tachypnea (16%), vomiting (14%), and cyanosis (6%). Apnea was not observed in any patient. Thirteen patients (26%) were asymptomatic (Table 1).

As laboratory findings, the most common hypoglycemia (40%), the second most common hypocalcemia (34%), and the third most common thrombocytopenia (26%) were found (Table 2).

Only partial exchange transfusion (PET) treatment was given to 25 patients (50%) and only medical treatment was given to 15 patients (30%). Both PET and medical treatment were given

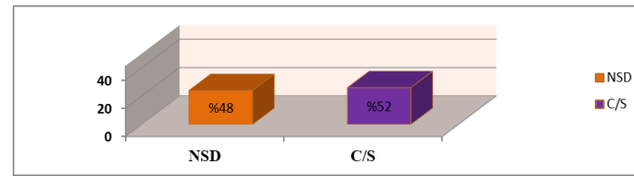

Figure 1. Distribution of polycythemic newborns by delivery type

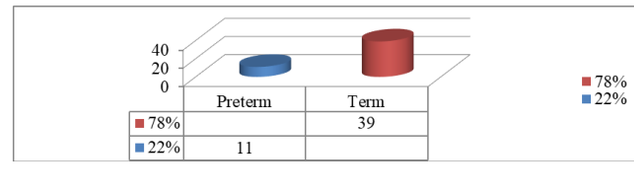

Figure 2. Term - preterm distribution of polycythemic newborns

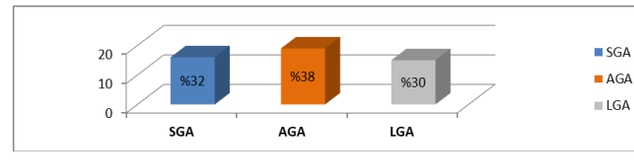

Figure 3. Birth weight for gestational age

Table 1. Symptoms of polycythemic newborns

	N	%
Jaundice	20	40.0
Tachypnea	8	16.0
Lethargy	11	22.0
Apnea	0	0.0
Cyanosis	3	6.0
Nonnutritive Sucking	13	26.0
Vomiting	7	14.0
Asymptonatic	13	26.0

Table 2. Laboratory findings of polycythemic newborns

	n	%
Hypoglycemia (<47 mg/dl)	17	34.0
Hypocalcemia (<8 mg/dl)	2	4.0
Thrombocytopenia (<150x103 mm³)	1	2.0
Normal laboratory findings	30	60.0

Table 3. Comparing the treatments algorithms in polycythemia

	n	%
PET	25	50.0
Medical treatment	15	30.0
PET+ medical treatment	1	2.0
Observation	9	18.0

to 1 patient (2%), and 9 patients were only observed (18%) (Table 3).

Discussion

In our study, the incidence of polycythemia in our unit was found to be 6,2% is higher than the previous studies [1-3]. So we can explain this result we found in this way that NICU population is sicker and has more risk factors for polycythemia than healthy newborns. Alfasadi et al.'s study in the Neonatal Intensive Care Unit supports this result that we found [6].

Our study showed that polycythemia is more common in males. Falih et al.'s study found results similar to the results of our study [14]. But, Barros et al. found that the distribution by gender was similar in their study [2]. However, this result we found needs to be supported by more studies.

When the birth patterns of newborns with polycythemia are examined, we see that birth rate by cesarean deliveries(C/S) was higher than normal spontaneous deliveries(NSD). There are different results in the literature regarding this. For exampel Alfasadi et al. found that similar finding [6]. But Falih et al. found an oposite result with us [14].

Neonates who were born at a gestational age less than 34 weeks have a lower risk of polycythemia than the terms [13-16]. In this study we found that it was 37.60±1.95 week with the ranges from 32 to 40 weeks. On the other side, Monzani et al. found in a similar studies that the mean gestational age was 39 week with a range 38-41 weeks [11]. Alfasadi et al. found the mean gestational age at 38.1 weeks [6].

In addition, Sarkar et al. said that polycythemia or hyperviscosity is rarely seen in premature infants less than 34 weeks [10]. In this study it was observed that 22% of polycythemic infants hospitalized in the NICU were preterm and 78% were term infants. And the mean weight was found to be 3015.50±991.11 g.

When we take a look for comparing the weight for the gestasional age, there is an agreement that SGA is a risk factor for the polycythemia [10-16]. But in our study, when neonates with polycythemia were examined, we found that 38% of them were mostly AGA babies. Although SGA is a risk factor for polycythemia, it should not be forgotten that it can also occur in infants with AGA.

Okeye et al.'s study showed that polycythemia group's APGAR scores with and without polycythemia at the first minute were 4.1±1.8 and 6.6±2.1, respectively and 5th minutes were 6.9±1.7 and 8.5±1.4 respectively. So they said that ''hematocrit correlated positively with Apgar scores (both at one and five minutes) in cases without polycythemia. Hematocrit of polycythemic newborns did not correlate with Apgar scores'' [4]. In our study, we found that the mean APGAR scores at both the 1st and 5th minutes of the infants hospitalized in the NICU with polycythemia were above 7, therefore, it was weakly associated with the low APGAR score. However, more studies should be done to explain the relationship between polycythemia and Apgar.

Clinical manifestations are the result of affected multiple organ systems by the polycthemia [12, 14]. Some of these clinical features include vomiting, tremulousness, tachypnea, jaundice, apnea, cyanosis, nonnutritive feeding, lethargy, tremor, respiratory distress, seizures and irritability [3, 5]. Different studies report different results for the most common symptom. For example, Özdemir et al. said that the most comon symptom is hypoglycemia [9]. Özalkaya et al. find that the most common clinical finding is respiration distress in late premature group, and feeding difficulties in the term group [7]. Sarkar et al. showed that the most common symptom is jaundice [10].

40% of polycthemia infants in this study had jaundice were found. We thought that the cause of these symptom most probably due to the breakdown of an increased number of circulating red blood cells.

When we looked at the laboratory findings, we saw that the most common finding was hypoglycemia, in our study. Özalkaya et al. and sarkar found a similar result to ours [7, 10]. In adition, we found that the hypocalcemia is the second most common lab abnormality, which is reported in 24,7% of neonates who have polycythemia in a similar study [10].

Two modes of treatment have been described for polycythemia. First one is partial exchange transfusion (PET) and second one is conservative management with hydration [13]. Treatment for polycythemia is fraught with controversy even if the recommended therapy for symptomatic infants is hemodilution by PET [10]. We found that the partial exchange transfusion(PET) treatment was received to 50% patients.

Conclusion

The findings of this research suggest that certain neonatal characteristics such as gestational age, gender, apgar scores and birth weight can play a significant role in the development of polycythemia in newborns. The limitation of our study is that most polycythmic infants admitted to the NICU are accepted due to other conditions related to polycythemia, the symptoms of polycythemia are not specific to only polycythemia, and the cases are not followed up in terms of prognosis in the following periods. Overall, our study contributes to the body of knowledge on neonatal polycythemia and provides a foundation for further research.

Scientific Responsibility Statement

The authors declare that they are responsible for the article's scientific content including study design, data collection, analysis and interpretation, writing, some of the main line, or all of the preparation and scientific review of the contents and approval of the final version of the article.

Animal and Human Rights Statement

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or compareable ethical standards.

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Conflict of Interest

The authors declare that there is no conflict of interest.

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