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Partial exchange transfusion for neonatal polycythemia

Elif Özalkaya, Sevilay Topçuoğlu, Egemen Yıldırım, Tuğba Gürsoy, Fahri Ovalı, Güner Karatekin

Zeynep Kamil Hospital Neonatal Intensive Care Unit, Istanbul, Turkey

Summary

Aim: The aim of this study was to investigate the short term effects of partial exchange transfusion on the morbidity of preterm and term polycythemic neonates.

Material and Method: Late preterm and term infants with polycythemia hospitalized in Zeynep Kamil Maternity and Children's Training Hospital Neonatal Intensive Care Unit from January 2009 to May 2010 were evaluated retrospectively.

Results: One hundred-sixty-three of 16.000 infants who were born during the study period were hospitalized with a diagnosis of polycythemia. The incidence of polycythemia was 1%. Late preterm polycythemic (n=68/163; 41.7%) patients were divided into two groups as symptomatic (n=23/163; 14.1%) and asymptomatic (n=45/163; 27.6%) infants. Term polycythemic (n=95/163; 58.3%) patients were divided into two groups as symptomatic (n=21/163; 12.9%) and asymptomatic (n=74/163; 45.4%) infants. Partial exchange transfusion (PET) was performed in 102 patients. Of these infants, 18/102 (17.7%) were symptomatic late preterm, 23/102 (22.6%) were asymptomatic late preterm, 14/102 (13.7%) were symptomatic term and 47/102 (46%) were asymptomatic term infants. The number of patients who were treated medically (hydration) was 61. Of these patients 5/61 (8.2%) were symptomatic late preterm, 22/61 (36%) were asymptomatic late preterm, 7/61 (11.5%) were symptomatic term and 27/61 (44.3%) were asymptomatic term patients. Duration of hospitalization in the term symptomatic group and time to reach full enteral feeding in the asymptomatic term group were longer in patients in whom PET was performed. ($p<0.05$). There were four patients (2 preterm, 2 term) who developed NEC following PET.

Conclusions: Our results showed that PET influences duration of hospitalization and time to reach full enteral feeding and increases the risk of NEC in asymptomatic patients. We believe that more studies should be performed to determine the indications of PET in asymptomatic infants. *(Turk Arch Ped 2012; 47: 23-8)*

Key words: Polycythemia, exchange transfusion, newborn

Introduction

Polycythemia is defined as increased erythrocyte mass and hyperviscosity is defined as resistance which develops against blood flow (1). For the definition of hyperviscosity venous hematocrite (Hct) value is used, since viscometry is not used widely and erythrocyte mass contributes to viscosity with a high rate. When venous Hct exceeded 65% in the neonatal period, viscosity was found to be increased (1). Generally, partial blood exchange is performed in many centers in asymtomatic cases with a Hct value above 70% and in symptomatic cases with a Hct value above 65% for treatment of neonatal polycythemia (2). However, both diagnosis and treatment of hyperviscosity is controversial. Hyperviscosity which causes slowing of blood flow and disruption of organ perfusion is present in only 47.4% of polycythemic patients (3). In addition, partial blood exchange which is performed to decrease hyperviscosity was not observed to be beneficial for long-term neurodevelopmental status and there are studies showing that partial blood exchange carries a risk in terms of necrotizing enterocolitis (NEC) (4-8). The aim of this study was to evaluate the effects of clinical course, risk factors and partial blood exchange on short-term mortality and morbidity in polycythemic term and late premature patients.

Material and Method

In this study, term and late preterm patients who were hospitalized in Zeynep Kamil Maternity and Children's Education and Training Hospital Neonatal Intensive Care Unit between January 2009 and May 2010 because of polycythemia

Address for Correspondence: Elif Özalkaya MD, Zeynep Kamil Hospital Neonatal Intensive Care Unit, Istanbul, Turkey
E-mail: elifozalkay@gmail.com **Received:** 05.05.2011 **Accepted:** 10.05.2011

or who was diagnosed as polycythemia after being hospitalized were evaluated retrospectively. Inlet Hct value was obtained by microcentrifuging the venous blood taken from the antecubital region 6 hours after birth. Outlet Hct value was the venous Hct value measured 6 hours after partial blood exchange or medical treatment.

While polycythemic patients with a gestational age of 34-37 weeks constituted the late preterm polycythemic group, polycythemic patients with a gestational age above 37 weeks constituted the term polycythemic group. In our clinic, infants of diabetic mothers, small or large for gestational age infants and infants with intrauterine growth failure are screened for polycythemia. Polycythemia is evaluated by complete blood count 6 hours after birth. If hemoglobin value is 20g/dL or higher, Hct is measured in venous blood obtained from antecubital region by free flow using the method of microcentrifuge.

The diagnosis of asymptomatic polycythemia is defined as a venous Hct value above 65%. Symptomatic polycythemia is defined as at least one clinical (central nervous system (CNS) or cardiovascular system (CVS) or gastrointestinal system (GIS) or renal involvement) or laboratory finding in addition to a Hct value above 65%. Central nervous system findings were defined as hypotonia and lethargy, irritability and seizure. CVS findings were defined as tachycardia, tachypnea, respiratory distress, cyanosis, pletorrhea, cardiomegaly, pulmonary vascular fullness, pleural fluid and pulmonary hypertension. GIS findings were defined as poor sucking, vomiting and NEC. Renal involvement was defined as oliguria. Laboratory findings were defined as hypoglycemia (<40 mg/dl), hypocalcemia, thrombocytopenia (<150x109/L) and hyperbiluribinemia (9).

With these clinical definitions late preterm polycythemic patients were divided into two groups as symptomatic late preterm and asymptomatic late preterm infants and term polycythemic patients were divided into two groups as symtomatic term and asymptomatic term infants.

Partial blood exchange was performed in all symptomatic or asymptomatic subjects with a venous Hct value above 70% and in symptomatic subjects with a venous Hct value of 65-69%. In patients in whom no partial blood exchange was performed, intravenous fluid was administered for at least 6 hours with an appropriate amount for age as medical treatment.

Partial blood exchange was performed via umbilical vein. The amount of physiological saline was calculated with the following formula: blood volume x (Hct of the patient-desired Hct)/Hct of the patient. The blood volume of the infant was considered to be 80-90 ml/kg in term infants and 90-100 ml/kg in preterm infants. It was aimed to decrease venous Hct to 55% with blood exchange (9).

Table 1. Demographic characteristisc, clinical findings and risk factors in term subjects

Term infants N=95	Symptomatic N=21 (22.1%)			Asymptomatic N=74 (77.8%)		
	Partial blood exchange N=14 (14.7%)	Medical N=7 (7.3%)	p	Partial blood exchange N=47 (49.4%)	Medical N=27 (28.4%)	p
Demographic charactersistics						
Birth weight (g)	2778±751	2474±293	>0.05	2693±610	2805±810	>0.05
Birth week (w)	38.7±1.58	37.7±0.76	>0.05	38.3±1.44	38.6±1.11	>0.05
C/S n (%)	12 (85.7)	4 (57.1%)	>0.05	35 (74.4%)	19 (70.3%)	>0.05
F/M (n)	6/8	4/3		26	17	
Risk factors n (%)						
Chronic hypoxia 29 (30,3)	2 (14)	2 (28)	>0.05	12 (25)	13 (47)	<0.05
Transfusion 3 (3,2)	-	-	-	1 (2)	2 (6)	>0.05
Chromosome anomaly and hypothyroidism 10 (10,5)	7 (49)	1 (14)	>0.05	2 (4)	-	>0.05
Clinical findings n (%)						
CNS	-	-	-			
CVS	-	-	-			
GIS 3 (3)	2 (14)	1 (14)	>0.05			
Renal	-	-	-			
Hyperbilirubinemia 1 (1)	1 (7)	-	>0.05			
Thrombocytopenia 15 (15,7)	9 (64)	6 (42)	>0.05			
Hypoglycemia 6 (6,3)	4 (28)	-2 (28)	>0.05			
Hypocalcemia	-	-	-			

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Demographic characteristics and risk factors of the patients hospitalized because of polycythemia, their clinical and laboratory findings before partial blood exchange, morbidity developed after blood exchange (hospitalization time, time to switch to enteral feeding, clinical sepsis, NEC) were evaluated retrospectively from the patient files. Risk factors were defined as chronic hypoxia (intrauterine growth failure, placental failure, preeclampsia and maternal smoking), blood transfusion (late clamping of the umbilical cord, transfusion between twins, transfusion from the mother to the infant or maternal diabetes), congenital syndromes (trisomy 13, 18, 21) and hypothyroidism (1).

Chi-square and stuıdent-t tests were used for statistical analysis of the data obtained in the study (SPSS for Windows version 15).

Results

Polycythemia was found in 163 of 16000 infants born during the study and the incidence of polycythemia was found to be 1%. The distribution of the patients by groups is shown in Table 1 and demographic characteristics, risk factors and clinical features are shown in Table 2 and Table 3. The effect of blood exchange on the rates of mortality and morbidity is shown in Table 4.

No statistically significant difference was found between the subjects in whom partial blood exchange was performed and the subjects who received medical treatment in terms of demographic charactersitics (symptomatic or asymptomatic). When the subjects were evaluated in terms of presence of risk factors (chronic hypoxia, transfusion, chromosomal anomaly and hypothryoidism), chronic hypoxia was found with a significantly lower frequency in the asymptomatic group in whom partial blood exchange was performed compared to the group who received medical treatment. In term polycythemic patients, the fact that “small for gestational age”(SGA) was in the forefront shows that chronic hypoxia is the most common risk factor causing polcysthemia.

No statistically significant difference was found between the symptomatic term infants in whom partial blood exchange was performed and the infants who received medical treatment in terms of clinical findings. In all term subjects, the most prominent clinical finding was feeding difficulty and the most common laboratory finding was thrombocytopenia.

When the short-term morbidity and mortality rates of partial blood exchange were evaluated, inlet Hct was found to be

Table 2. Demographic characteristisc, clinical findings and risk factors in preterm infants

Preterm infant N=68	**Symptomatic N=23 (33.8%)**			**Asymptomatic N=45 (66.1%)**		
	Partial blood exchange N=18 (26.4%)	**Medical N=5 (7.3%)**	**p**	**Partial blood exchange N=23 (33.8%)**	**Medical N=22 (32.3%)**	**p**
Demographic characteristics						
Birth weight (g)	2095±365	2380±200	>0.05	2254±351	2378±331	>0.05
Birth week (w)	34.6±1.5	35.4±1.3	>0.05	34.55±1.01	34.55±1.44	>0.05
C/S n (%)	13	2		18	15	
F/M (n)	9/9	3/2		11	10	
Risk etmenleri n (%)						
Chronic hypoxia 13 (19)	5 (27)	-	>0.05	4 (17.3)	4 (18)	>0.05
Transfusion	-	-		-	-	>0.05
Chromosome anomaly and hypothyroidism 3 (4)	1 (5)	-	>0.05	2 (8)	4 (18)	>0.05
Clinical findings n (%)						
CNS	-	-	-			
CVS 6 (8)	6 (33.3)	-	>0.05			
GIS 2 (3)	1 (5.5)	1 (20)	>0.05			
Renal	-	-	-			
Hyperbilirubinemia 3 (4.4)	2 (11)	1 (20)	>0.05			
Thrombocytopenia 6 (8.8)	3 (16.6)	3 (60)	>0.05			
Hypoglycemia 10 (14.7)	7 (38)		>0.05			
Hypocalcemia 1 (1.4)	1 (5)	-	>0.05			

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Table 3. The effect of partial blood exchange on the rates of morbidity and mortality in preterm infants

Preterm infant N=68	Symptomatic N=23 (33.8%)			Asymptomatic N=45 (66.1%)		
	Partial blood exchange N=18 (26.4%)	Medical N=5 (7.3%)	p	Partial blood exchange N=23 (33.8%)	Medical N=22 (32.3%)	p
Inlet Hct (mean)	73.5±3.5	68.6±4.5	<0.05	73.13±3.06	69.32±2.4	<0.05
Outlet Hct (mean)	55±5.73	64.4±2.1	<0.05	55.8±3.60	60.8±4.4	<0.05
Time to switch to enteral feeding (mean)	3.82±2.32	3.2±1.79	>0.05	2.3±1.5	1.91±1.1	>0.05
Hospitalization time (mean)	7.7±3.5	6.2±1.7	>0.05	5.57±1.75	4.68±2.48	>0.05
NEC n (%)	-	-	-	2 (8.6)	-	>0.05
Clinical Sepsis n (%)	-	-	-	2 (8.6)	-	>0.05

Hct: hematocrite, NEC: necrotizing enterocolitis

Table 4. The effect of partial blood exchange on the rates of morbidity and mortality in term infants

Term infant N=95	Symptomatic N=21 (22.1%)			Asymptomatic N=74 (77.8%)		
	Partial blood exchange N=14 (14.7%)	Medical N=7 (7.3%)	p	Partial blood exchange N=47 (49.4%)	Medical N=27 (28.4%)	p
Inlet Hct (mean)	73.4±5.6	66.5±2.7	<0.05	72.3±2.76	69.2±3.11	<0.05
Outlet Hct (mean)	53.9±4.65	59.1±4.45	<0.05	55.6±4.32	61.85±4.4	<0.05
Time to switch to enteral feeding (mean)	3.00±1.62	3.00±1.41	>0.05	2.7±1.4	1.9±0.8	<0.05
Hospitalization time (mean)	7.36±2.71	5.0±1.15	<0.05	5.47±2.0	3.92±1.41	<0.05
NEC n (%)	-	-	-	2(2.7)	-	>0.05
Clinical sepsis n (%)	-	-	-	-	-	-

Hct: hematocrite, NEC: necrotizing enterocolitis

higher in term subjects (symptomatic or asymptomatic) in whom partial blood exchange was performed compared to the subjects who received medical treatment and outlet Hct value was found to be lower ($p<0.05$). Hospitalization time was longer in term subjects (symptomartic or asymptomatic) in whom partial blood exchange was performed compared to the subjects who received medical treatment ($p<0.05$). In symptomatic term subjects, partial blood exchange had no effect on the time to switch to enteral feeding, while the time to switch to enteral feeding was found to be longer in asymptomatic subjects in whom partial blood exchange was performed ($p<0.05$). NEC developed in two asymptomatic term subjects in whom partial blood exchange was performed, though it was not found to be not statistically significant compared to the asymptomatic term subjects who received medical treatment.

No statistically significant difference was found between the late preterm (symptomatic or asymptomatic) subjects in whom partial blood exchange was performed and the subjects who received medical treatment in terms of demographic characteristics. The most common risk factor in late preterm subjects was preeclampsia. The prominent clinical symptom was found to be respiratory distress and the most common laboratory finding was hypoglycemia. Inlet Hct value was found to be higher and outlet Hct value was found to be lower in late preterm subjects in whom partial blood exchange was performed compared to the subjects who received medical treatment (symptomatic or asymtomatic) ($p<0.05$). Hospitalization time and the time to switch to enteral feeding was found to be longer in all subjects in whom partial blood exchange was performed, though not statistically significantly. NEC developed in two asymptomatic subjects in whom partial blood exchange was performed.

Discussion

In this study, the incidence of polycythemia was found to be 1% similar to previous studies (2).

In the diagnostic and therapeutic decision for polycyhemia, risk factors or etiology should be evaluated together with venous Hct. Some neonatal units tailor the treatment according to the etiological factors: 1. Subjects with chronic hypoxia who have normal or decreased plasma volume along with increased erythrocyte mass (for example, intrauterine growth failure, placental failure, preeclampsia and maternal smoking). 2. Subjects with increased erythrocyte mass and increased plasma volume secondary to blood transfusion (delayed cord clamping, transfusion between twins, transfusion from the mother to the infant or maternal diabetes). 3. Subjects with congenital syndromes who have increased erythrocyte mass

and normal plasma volume (trisomy 13, 18, 21). Providing hydration instead of partial blood exchange is another therapeutic option in asymptomatic patients exposed to chronic hypoxia who develop polysthemia with decreased plasma volume and who have a venous Hct value of 70-75% (1). Morag et al. (10) showed that this therapeutic approach did not lead to increase in short-term complications of polycythemia. In this study, the most common risk factor in term and late preterm subjects was also found to be chronic hypoxia. The fact that chronic hypoxia was present in the etiology in 4 patients who developed NEC after partial blood exchange and that these patients were asymptomatic showed that the etiology should be evaluated before treatment decision.

The most common clinical findings in polysthemia include lethargy, tachypnea, tremor, irritability, poor feeding and vomiting. The most common laboratory finding is hypoglycemia (2). When Gross et al. (11) evaluated 18 polycythemic patients, cyanosis and hyperbilirubinemia were found to be the most common findings. Ramamurthy and Brans (12) found plethorrhea to be the most common finding in 54 patients. Black et al. (13) found hypoglycemia to be the most common finding in 111 patients and Goldberg (4) found cardiomegaly and hypoglycemia to be the most common findings. In our study, the most common clinical finding was found to be respiratory distress in late preterm patients and feeding difficulty in term patients. The most significant laboratory finding was found to be thrombocytopenia in term subjects and hypogycemia in late preterm subjects. Clinical findings are not specific. When the distribution of the findings were evaluated, the high frequency of laboratory findings was noted. Treatment criteria should include the association of at least one clinical finding and one laboratory finding instead of one clinical finding or one laboratory finding.

The treatment method in polycythemia is partial blood exchange which provides hemodilution. It improves clinical findings related to hyperviscosity, increases the blood flow in the brain, decreases vascular resistance in the lung and corrects hypoglycemia. The decision of partial blood exchange which is not controversial in symptomatic patients is controversial in asymptomatic patients.

Neurologic findings in polysthemia are thought to be arised as a result of decreased blood flow in the brain. Studies have shown that blood flow and microcirculation improved after partial blood exchange using Doppler ultrasonography and “near infrared” spectroscopy (14,15). However, some studies suggested that partial blood exchange did not contribute to neurological improvement in the neonatal period or in the long-term in symptomatic or asymptomatic infants (4-7,16,17).

The second risk in partial blood exchange which is being discussed is the increase in the frequency of NEC. Although polycythemia alone can cause NEC, there are studies which showed that partial blood exchange was a more significant risk factor for NEC. Black et al.(18) found GIS symptoms with a rate of 6% in untreated polycythemic patients and with a rate of 51% in patients in whom partial blood exchange was performed. In this study, the risk factor for NEC was partial blood exchange, but not polycythemia. Hopewell et al. (8) found that the frequency of NEC increased with partial blood exchange in polycythemic patients. In a metaanalysis performed by Özer et al.(16), it was found that partial blood exchange had no positive effect on neurologic development in the short-term (symptoms) or long-term in symptomatic or asymptomatic polycythemia and carried a risk in terms of NEC. In our study, mean hospitalization time and mean time to switch to enteral feeding was found to be longer in asymptomatic term subjects in whom partial blood exchange was performed compared to the subjects who received medical treatment ($p<0.05$). In addition, NEC, clinical sepsis and exitus occured in two late preterm asymptomatic subjects in whom partial blood exchange was performed and NEC and sepsis occured in two term asymptomatic subjects, though not statistically significant.

In practice, some neonatal untis continue to consider a venous Hct value of 70% as the cut-off level for partial blood exchange in asymptomatic patients, while many units developed a new therapeutic approach considering the etiology. Some approaches recommend the following: If Hct is 70-75% and polycythemia is associated with decreased blood volume, early feeding or enlargement of the plasma by intravenous serum physiologic. If there is increased blood volume, cardiovascular monitorization and glucose monitorization. If the blood volume is normal and recurrent measurements show a Hct value above 75%, partial blood exchange. (1,10). In our study, the fact that there were no risk factors in four subjects in whom NEC developed after partial blood exchange and these patients were asymptomatic was notable. Therefore, the etiology should be evaluated primarily in asymptomatic polycythemia and the decision of partial blood exchange should be made considering that it has no effect on NEC and neurological development.

Conclusively, the justifications for partial blood exchange should include the presence of at least one risk factor and the association of one clinical and one laboratory finding. In our study, it was shown that partial blood exchange prolonged the hospitalization time and the time to switch to enteral feeding and carried a risk for NEC, when the only justification for partial blood exchange was a Hct value above 70% in asymptomatic polycythemia. In addition, the studies in the literature which reported partial blood exchange had no effect on neurological development in the long-term suggest that new studies are needed to determine the presence of risk factors for a decision of partial blood exchange in asymptomatic polycythemia and to determine the limit of venous Hct. Until a consensus is instituted, determination of the justifications of partial blood exchange according the risk factors (a. If the risk factor is decreased blood volume, early feeding or administration of intravenous physiological saline, b. If the risk factor is increased blood volume, cardiovascular monitorization and glucose monitorization, c. If the blood volume is normal and repeated measurements show a Hct value above 75%, partial blood exchange) defined in the literature is acceptable because of its effect to decrease the risks of blood exchange.

Conflict of interest: Not reported.

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