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REVIEW

THE EFFICACY OF PARTIAL EXCHANGE TRANSFUSION IN NEONATAL POLYCYTHEMIA

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ABSTRACT

Polycythemia is defined as a central venous hematocrit level of more than 65%. Polycythemia occurs because of increased red cell mass, with decreased, normal, or increased plasma volume. On the other hand, hyperviscosity of blood results in increased resistance to blood flow and decreased oxygen delivery. Both polycythemia and hyperviscosity can cause central nervous system dysfunction, hypoglycemia, impaired renal function, and cardiorespiratory distress. Hyperviscosity has also been reported to be associated with long-term neurodevelopmental disorders in childhood. Polycythemia and hyperviscosity are related to alterations in organ perfusion. There is a decrease in end-organ blood perfusion due to changes in red cell mass, arterial oxygen content, and/or viscosity. There are two main treatment approaches to neonatal polycythemia. The first approach is restrictive management, whereas the second approach is partial exchange transfusion, a more controversial one. Partial exchange transfusion is a procedure in which the blood of the infant is diluted. Various studies have had outcomes suggesting no clinically significant short and long-term benefits of the partial exchange transfusion, especially in asymptomatic infants and infants with minor symptoms. However, it is crucial to note that there are no long-term follow-up studies to evaluate the neurodevelopmental status of infants with neonatal polycythemia. In contrast to partial exchange transfusion, restrictive management has been confronted with several difficulties. Therefore, further controlled studies with new methods are needed to observe the long-term effects. In this review, it is aimed to evaluate the efficacy of current and recently retrieved treatment approaches in neonatal polycythemia.

Keywords: Exchange transfusion, hyperviscosity, neonatal polycythemia, newborn, NIRS

INTRODUCTION

Neonatal polycythemia is a condition that has been studied for years to understand neonatal mortality and morbidity due to its assured adverse effects such as delay in neurodevelopment and organ dysfunction yielding renal failure with uncertain treatment success (1, 2). It is characterized by a central venous hematocrit (HCT) level of more than 65%. This threshold was set based on the observation of the exponential increase of blood viscosity after a HCT level of 65% (3). HCT level varies based on the location of blood samplings such as an umbilical vein, peripheral vein, or capillary blood, the age of the newborn at the time of assessment, and the method of processing the blood. In different settings, polycythemia and hyperviscosity are used interchangeably. Polycythemia occurs due to increased red blood cell mass with varying plasma volumes (4). On the other hand, hyperviscosity of the blood leads to increased resistance to blood flow and decreased tissue oxygenation due to decreased delivery. Hyperviscosity can induce organ dysfunction such as central nervous system dysfunction, hypoglycemia, impaired renal function, and cardiorespiratory symptoms (5). Furthermore, it predisposes to stasis in microcirculation, which may result in further hematological disorders (6). Hyperviscosity has also been attributed to long-term neurodevelopmental disorders in children (7, 8). Thus, this review aims to evaluate the efficacy of current and recently retrieved treatment approaches in neonatal polycythemia.

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Incidence

It occurs in 0.4% to 5% of normal weight infants but may rise to 15% in infants small for gestational age (SGA) and 20% in infants large for gestational age (LGA) (9-15). It is less likely in preterm infants with a gestational age under 34 weeks (6, 16). Furthermore, neonates from twin pregnancies are considered to retain a higher risk of polycythemia (17). It is also previously stated that four percent of neonatal polycythemia cases are associated with trisomy 21. A similar observation is noted for the infants with trisomy 21, as neonatal polycythemia is one of the most common hematological abnormalities. High cord blood erythropoietin concentration is assumed to be the reason in affected infants with trisomy 21, which could indicate intrauterine hypoxemia involvement (18, 19).

Risk Factors

It has been mentioned before that preterm infants under 34 weeks are less likely to have polycythemia or hyperviscosity, however, SGA and LGA infants are more prone to have neonatal polycythemia (1). Increased fetal erythropoiesis, red blood cell count, HCT level, and blood viscosity may arise from fetal hypoxia. Chronic fetal hypoxia can be driven by fetal and maternal factors. Pregnancy-related conditions that may result in chronic fetal hypoxia include fetal hyperthyroidism, pre-eclampsia, maternal diabetes, and maternal smoking. There are some other pregnancy-related risk factors such as milking or delayed clamping of the umbilical cord. Milking the umbilical cord toward the neonate may lead to substantial polycythemia, particularly if the newborn is being kept below the level of the placenta (20). Another randomized controlled research has confirmed that late cord clamping instead of early cord clamping (<30 seconds) results in increased HCT levels in both preterm and term newborns (21). However, the benefits of late cord clamping in infant health have been clearly shown and far outweigh the theoretical risk of polycythemia (22, 23). Organ dysfunction as a result of polycythemia and hyperviscosity is related to changes in perfusion. End-organ blood perfusion is reduced because of the abnormalities in red blood cell mass, arterial oxygen content (CaO_2), and/or viscosity (2). Interestingly, clinical signs and symptoms of hyperviscosity may impair the crucial maternal-infant bonding in the first hours of life (24).

Treatment

There are two main approaches for the treatment of neonatal polycythemia. The first approach is restrictive management via hydration and fluid supplementation, keeping the infant warm, nutritional management, and cardiorespiratory monitorization. While partial exchange transfusion (PET) is preferred in symptomatic infants with polycythemia and asymptomatic infants with HCT levels higher than 70%, restrictive management is more confined to asymptomatic infants. PET is a procedure in which the blood of the infant is diluted. It has been demonstrated to decrease pulmonary hypertension, increase cerebral blood perfusion, and improve hypoglycemia and 83 renal function (2). Yet, there are some controversies over PET. Necrotizing enterocolitis (NEC) is a raised concern as the most pronounced complication of PET (25). However, it is questioned whether NEC is the consequence of blood hyperviscosity or the procedure itself (26). The main objective of PET is to preserve circulatory volume while lowering the HCT level and hyperviscous status. The amount of blood to be exchanged is determined by using the formula below:

Volume to exchange = the total blood volume of baby *x (observed HCT - desired HCT)/observed HCT.

*The total blood volume of a baby is taken as 80-90 mL/kg in term babies and 90-100 mL/kg in preterm babies.

In the systematic review of Ozek et al. (5) about the efficacy of PET in neonatal polycythemia to prevent neurodevelopmental disorders, seven randomized controlled or quasi-randomized clinical trials comparing PET to controls in infants with neonatal polycythemia were reviewed. In one of these clinical trials, the effects of PET in neonates in terms of their neurobehavioral status were investigated (2). They divided the neonates into three groups. Of the two groups with neonatal polycythemia, one received the transfusion treatment. The third one was a healthy control group. They compared the effect of transfusion treatment to non-treatment using the Brazelton Neonatal Behavioral Assessment Scale and Neurological Assessment of Prechtl. The examination was performed at 10 days of age. Although a behavioral discrepancy between the transfusion treatment and the control groups was noted, there was no pronounced neurodevelopmental difference among the three groups. At 8 months of age, the infants were finally examined using a scale that is similar to Griffiths Developmental Score. The results were not significantly different between the affected groups who received either PET or not, including the ones who had been considered abnormal earlier. Furthermore, the children in this study were monitored until they reached school-starting age. Their developmental performance was appropriate when they were last seen, which was at two years of age. The significant aspects of the study were that before this study, hypocalcemia and hypomagnesemia were not taken into consideration in hyperviscous newborns. However, the information on the timing of the transfusion and hyperviscosity status of the non-treatment group might be noted as limitations (2). Goldberg et al. (27) studied symptomatic polycythemic infants, dividing them in two groups as either observation or PET treatment. Infants receiving exchange transfusions subsequently improved, whereas the observation group was slower in terms of neurological improvement up to 3 weeks of life. Nevertheless, at 8 months of age, abnormal neurological and developmental findings were no longer present in either group. Lastly, the study carried out by Black et al. (25) showed that the later neurodevelopmental impairments and/or delays were more likely to be seen in the untreated group at some uncertain time of life. Kumar and Ramji (28) examined the effects of PET in fifty-five asymptomatic polycythemic low birth weight (LBW) babies to modify neonatal morbidity and

mortality. Developmental delays using Denver Developmental Screening Test-II, neurological deficits, tone, and deep tendon reflex abnormalities were evaluated over an 18-month follow-up period. It was concluded that neonatal morbidity in asymptomatic polycythemic LBW babies was low and was not influenced by PET (28). Various studies, aforementioned in this systemic review, have had similar outcomes suggesting no significant short and long-term clinical benefits of PET, especially in asymptomatic infants and symptomatic infants with minor symptoms. Additionally, there might be a risk of NEC due to PET. However, it is crucial to note that there is no long-term follow-up study to perceive the neurodevelopmental status of infants with neonatal polycythemia (16, 29-30). On the other hand, restrictive management has been confronted with several difficulties. The first question about the intervention is the threshold of the HCT level. There is a recent study that divided infants into three groups according to their HCT levels (31). Each group included not only symptomatic but also asymptomatic infants. They applied PET to the symptomatic infants independent of their HCT levels (only more than 65% level), whereas asymptomatic infants received hydration with glucose 10% solution, up to HCT levels of 75%. After a 75% level of HCT, asymptomatic infants also received PET restrictive approach and were not associated with increases in short-term neonatal morbidities. The authors concluded that restricting PET to a higher threshold (>75%) in asymptomatic polycythemic newborns did not raise the risk of early neonatal morbidities (31). In contrast to restrictive management, there is a recent approach that suggests no fluid supplementation at all. It should be noted that such an approach has been reported to be effective when HCT levels are up to 75% in asymptomatic newborns with polycythemia (32). Although randomized studies have been done about treatment and neonatal polycythemia so far, local protocols and regional guidelines are based on whether a patient is asymptomatic or symptomatic, there is no international or universal consensus. In symptomatic patients, PET is preferred at 65% HCT, while in asymptomatic children, monitorization and a conservative approach are recommended at the same level of HCT. Especially in asymptomatic children, the threshold can be considered 70 to 75% of HCT (33-35).

Monitorization of the Effects of PET on the Central Nervous System

In infants with polycythemia, Doppler techniques were utilized to show reduced cerebral blood perfusion in normal ranges after PET (2, 16, 36). In addition, with the use of Doppler ultrasound, one can conclude that increased cerebral arteriolar diameter might explain why some infants with polycythemia become asymptomatic (16). A relatively recent study showed the effects of PET on cerebral oxygenation and peripheral microcirculation in neonates with polycythemia using Near-Infrared Spectroscopy (NIRS) and Sidestream Dark Field (SDF) (37). It was the first study to use NIRS to explore the effects of PET on cerebral oxygenation and microcirculation in neonates with polycythemia. PET caused a considerable increase in cerebral oxygenation and faster microcirculation, as measured by NIRS and SDF techniques, respectively. Despite the limited research and inadequate data on better long-term prognosis in neonates who received PET, increased cerebral oxygenation is a potentially desirable impact in favor of PET. Further research is required to determine the consequences of faster microcirculation following PET in this patient population (36, 37).

CONCLUSION

In clinical settings, a higher HCT threshold (>75%) for asymptomatic infants has been demonstrated to be applicable since it did not indicate an increased risk for early neonatal morbidities (31). However, in asymptomatic newborns with polycythemia, the treatment aspects require further study as fluid supplementation may not reduce the need for PET in this population (32). On the other hand, symptomatic newborns with polycythemia can be treated by PET with a favorable outcome (27, 36, 38). There are some morbidities such as hypocalcemia, hypomagnesemia, and respiratory distress attributed to polycythemia and hyperviscosity (2, 5, 39). Thus, in symptomatic newborns, short-term morbidity and mortality rates were decreased with PET treatment (2, 16, 25-30, 38). Yet, there might be some misconceptions, such as the attribution of hypoglycemia to polycythemia, for evaluating neonatal morbidity and mortality (39). Therefore, further controlled studies with new methods, such as NIRS, are needed to observe long-term effects.

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