Clinical Medical Reviews and Case Reports

Neonatal Polycythemia: A Review

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Abstract

Polycythemia in the newborn is defined as either venous hematocrit or hemoglobin levels above 65% and 22 g/dl, respectively. Its incidence is reported between 1 to 5%. In this article definition and epidemiology of polycythemia, physiological changes in postnatal hematocrit levels, relationship between polycythemia and hyperviscosity, pathophysiology and diagnosis of polycythemia, etiology, clinical signs and complications of polycythemia with a special emphasis on treatment algorithms and long-term neurodevelopmental outcome considering all current review articles and meta-analyses are reviewed.

Keywords

Hyperviscosity, Newborn, Polycythemia, Partial exchange transfusion

Introduction

Definition and epidemiology

Polycythemia in the newborn is defined as either venous hematocrit or hemoglobin levels above 65% and 22 g/dl, respectively [1-4]. Its incidence is reported between 1 to 5% [3-8]. Its risk is higher in newborns born to mothers living in high altitudes whereas the risk decreases in premature newborns born before 34th week of gestation [9-11].

Physiological changes in postnatal hematocrit levels

Hematocrit levels increase in comparison to cord levels making a peak at around 2nd hour of life and a plateau between 2-4 hours of life, and then return to cord blood levels at 12 to 18 hours of life. The postnatal age at which newborns are screened for polycythemia is, thus, very important with this respect. The incidence of polycythemia may increase up to 20% when screened at 2nd hour whereas its incidence may be detected as low as 2% when its screening is performed at 12 to 18 hours postnatally [12].

Capillary and venous hematocrit measurements

Hematocrit measurement can be made in both capillary and venous samples. However erythrocyte concentration and the ultimately measured hematocrit level show a great variability depending on the route where the blood sample is obtained. Hematocrit measurement in capillary samples gives higher results in comparison to venous samples because of the rouleaux formation and migration of erythrocytes along the vascular wall, and sensitivity to variations in blood flow [9].

Due to the variations in and weaknesses of capillary measurement, gold standard blood sample to be used in the diagnosis of polycythemia is venous blood sample. In general hematocrit level in capillary samples is found 5-15% higher than that in venous samples, and hematocrit level in peripheral blood samples is higher than that in central venous samples. In a study conducted on newborns with a peripheral venous hematocrit level of ≥ 65%, capillary, peripheral venous and central (umbilical) venous hematocrit levels were reported as 75%, 71% and 63%, respectively [4]. In parallel with this finding, only 3-5% of newborns diagnosed to have polycythemia on screening with capillary measurements were found hyperviscosis [3,13,14], whereas approximately 50% of newborns detected as polycythemic in umbilical cord blood samples had hyperviscosity [15].

Warming the heel before obtaining capillary sample via heel-stick may aid in providing a closer correlation between the measurements of capillary and venous blood samples. Capillary samples may be used for screening, however all high values should be confirmed by a venous sample for the diagnosis of polycythemia [10,11] since approximately 18% of those tested and misdiagnosed with an incorrect method at 2nd hour of life would be subjected to a potential harmful and expensive treatment [12].

Methods of Hematocrit Analysis

Two methods are available

Automatized hematologic analysis: Hematocrit value is indirectly calculated from mean corpuscular volume and hemoglobin values in automatic blood analyzers.

Micro-centrifuge method: Blood is collected into heparinized microcapillary tubes and centrifuged at 10000-15000 rpm for 3-5 minutes. Plasma is separated and packed red cell volume is measured to give the hematocrit. An automatized analyzer gives lower values when compared to the centrifugation method [11]. In most of the studies conducted about polycythemia, centrifugation method has been used.

Relationship between Polycythemia and Hyperviscosity

Hyperviscosity and polycythemia are different definitions although they are often used interchangeably. Polycythemia is the abnormal increase in erythrocyte mass, and defined as a venous hematocrit level of > 65% in newborns. Viscosity is, on the other hand, the property of the liquid which provides the resistance of that

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Table 1: Etiology of neonatal polycythemia [22].

Erythrocyte transfusion (Passive)
Delayed clamping of umbilical cord
Uncontrolled or precipitous delivery
Intrapartum hypoxia
Twin-to-twin transfusion (In 10-15% of monochorionic twins)
Materno-fetal transfusion
Increased intrauterine erythropoesis (Active)
Plasental insufficiency
Preeclampsia
Other hypertensive disorders
Other vascular problems
Maternal hypoxemia due to cardiac or pulmonary diseases
Cardiac and pulmonary disorder
Drugs (i.e. propranolol)
Smoking
High altitude
Postmaturity
Diseases associated with fetus
Large-for-gestational age newborns
Maternal diabetes mellitus
Beckwith-Wiedemann syndrome
Endocrine disorders (Congenital adrenal hyperplasia, hypothyroidism, hyperthyroidism)
Chromosomal disorders (Trisomi 21,18 and 13)

liquid against placing between the two layers of the fluid. Viscosity equals to the ratio of powers effective on the unit square of the liquid or sliding tension to sliding velocity. Sliding resistance of the liquid or its response to changes in sliding velocity is somewhat different from other liquids as whole blood is not a homogenous liquid [9]. The relationship between hematocrit and viscosity is linear below the hematocrit levels of 60%, whereas progressive increases over 65% show a logarithmic relationship [4,13]. This means even a small increase in hematocrit over the levels of > 65% causes a dramatic increase in viscosity. Hyperviscosity is the decrease of blood fluidity, and defined as a viscosity above the 2 standard deviation of the mean. Hyperviscosity syndrome, on the other hand, is a syndrome of circulatory disorder developing secondary to increase in resistance against blood flow [9,11]. Except for the hematocrit level, there are a lot of factors affecting whole blood viscosity. Leukocytes, platelets, plasma proteins, immunoglobulins and coagulation factors are the other cellular elements which affect the whole blood viscosity. Hyperviscosity has been detected in 47% of newborns with polycythemia [15], whereas polycythemia has been detected as the etiologic factor in only 24% of newborns with hyperviscosity [11,15,16]. It is not easy to measure viscosity, and Wells-Brookfield viscometer is used with this aim. However most of the neonatal intensive care units do not have this device, and high hematocrit level and the presence of polycythemia-associated symptoms are taken into account as the determinator of hyperviscosity [9,11].

Pathophysiology

Polycythemia may cause some symptoms and complications due to the metabolic and hemodynamic effects of hyperviscosity, microcirculatory hipoperfusion, decreased organ blood flow and multisystem organ dysfunction, destruction of increased erythrocyte mass, and hyper/hypovolemia. Tissue hypoxia, acidosis and hypoglycemia develop secondarily to regional effects of hyperviscosity. Tissue blood supply and oxygenation are disrupted. Oxygen carrying capacity is determined by the hemoglobin level and blood flow, it is optimal at the normal hematocrit levels, and oxygen transport is decreased at low hematocrit levels as the oxygen binding capacity decreases [17]. Increase of blood volume, while the hematocrit is the same, increases blood flow and oxygen transport by decreasing peripheral vascular resistance with vasodilatation. This mechanism constitutes the basis of treatment of polycythemia [7]. With polycythemia/hyperviscosity, decreases in cerebral blood flow, arterial glucose concentration, cerebral glucose up take and disturbed cerebral glucose distribution have been reported [17,18].

Decreased microcirculation has been deemed responsible for the morbidity associated with polycythemia. Thrombi ocurring in microcirculation may cause symptoms in central nervous system, kidneys, surrenal glands, cardiopulmonary and gastrointestinal systems [19]. Drew, et al. [15] have demonstrated that the primary factor determining the neurological prognosis in polycythemia/hyperviscosity syndrome is hyperviscosity [20]. As a conclusion perfusion and tissue oxygenation are disturbed, plasma glucose concentration decreases, cerebral glucose uptake is disturbed and risk of cerebral morbidity is increased with microthrombi formation as the viscosity increases [7,17,21]. In neonatal polycythemia increased destruction of increased erythrocyte mass with a relatively shorter erythrocyte life span primarily contributes to hyperbilirubinemia. Hypervolemia may lead to congestive heart failure, pulmonary edema and cardiopulmonary failure, and hypovolemia may cause hypoxic-ischemic organ injury [12].

Etiology

Although the etiology of polycythemia is multifactorial, there are two primary mechanisms: passive (erythrocyte transfusion) and active (increased intrauterine erythropoiesis) (Table 1) [22]. Polycythemia secondary to excess erythrocyte transfusion to the fetus (Passive polycythemia) may occur due to delayed clamping of the cord, acute fetal distress and intrapartum hypoxia, twin-to-twin transfusion syndrome, materno-fetal transfusion and holding the baby below the level of introitus [9,11].

In acute fetal distress and peripartum hypoxia transcapillary leakage of plasma occurs and blood flow from placenta to fetus increases, and all these result in increased plasma volume and erythrocyte mass in the fetus [9]. Clamping of the umbilical cord later than 3 minutes after delivery of the baby is defined as "delayed cord clamping" [11]. Carpasso, et al. (2003) have reported a significant decrease in the incidence of polycythemia in newborns whose umbilical cord was clamped early (in first 10 seconds of life) when compared to those whose umbilical cord was clamped late (in 11th to 120th seconds of life) [23]. Therefore, early cord clamping and holding the baby at the level of introitus at the time of delivery could play a role in prevention from polycythemia by minimizing materno-fetal transfusion. On the other hand, however, no statistically significant differences were reported in the hematocrit values of newborns whose umbilical cord was clamped early or late [24]. Twin-to-twin transfusion syndrome is seen in approximately 10% of recipients of monochorionic twins [25].

Polycythemia secondary to increased intrauterine erythropoiesis (active polycythemia) is usually observed in cases of placental insufficiency, intrauterine hypoxia and situations associated with the fetus. Maternal hypertension [26], preeclampsia, maternal diabetes mellitus (type 1 diabetes mellitus and gestational diabetes) [27], maternal cyanotic heart disease, intrauterine growth retardation, postmaturity, living at high altitude and maternal smoking are all associated with this mechanism.

Situations associated with fetus may develop secondarily to problems either in fetus or maternal diseases (Table 1). The incidence of polycythemia in newborns of diabetic mothers varies between 22 to 29%, and polycythemia shows a close correlation with macrosomia and neonatal hypoglycemia in these babies [9,11]. There is an increased risk of polycythemia in diseases with a genetic inheritance such as trisomy 18 and trisomy 13 [28], trisomy 21 [29], and Beckwith-Wiedemann syndrome. Congenital hypothyroidsm, neonatal thyrotoxicosis and congenital adrenal hyperplasia are the other causes of polycythemia associated with the fetus [9,11].

Another etiologic classification of polycythemia is the one based on the volume status of plasma: normovolemic, hypervolemic and hypovolemic [12].

Normovolemic polycythemia

There is an increase in erythrocyte mass while intravascular volume is normal. It is seen in intrauterine growth retardation, maternal hypertension, maternal diabetes mellitus, and in situations

associated with placental insufficiency and/or chronic intrauterine hypoxia such as maternal smoking and postmaturity.

Hypervolemic polycythemia

There is an increase in plasma volume in association with an increased erythrocyte mass. It is usually seen in cases of acute transfusion such as maternofetal transfusion and twin-to-twin transfusion.

Hypovolemic polycythemia

It is due to the relative increase of erythrocyte mass in comparison to plasma volume. This situation usually develops due to intravascular dehydration [12].

Clinical Signs and Complications

Most of the newborns (74-90%) are asymptomatic [30,31]. In symptomatic newborns polycythemia may affect many organs and systems. Hyperviscosity, decrease of tissue perfusion, and metabolic complications such as hypoglycemia and hypocalcemia are responsible for clinical signs [10,32]. Nonspecific signs and symptoms such as apnea, cyanosis, feeding problems, vomiting, irritability, jitteriness,

tremor, lethargy, respiratory distress and seizures may be seen [16]. The most commonly encountered problems in severely symptomatic newborns with polycythemia are central nervous system disorders [11,32,33].

Cardiopulmonary complications (Cardiomegaly, increase in pulmonary vascular resistance and decrease in cardiac output) with tachycardia and tachypnea may develop [32].

Although polycythemia and hyperviscosity have been suggested responsible for the pathogenesis of necrotizing enterocolitis in term and near-term newborns [34,35], partial exchange transfusion itself, performed to lower the hematocrit, has been reported to cause necrotizing enterocolitis [36-38].

Renal problems encountered in polycythemia are decrease in glomerular filtration rate, oliguria, hematuria, proteinuria and renal vein thrombosis [16,39].

Of the metabolic problems, the most commonly encountered is hypoglycemia (12-40%). In addition to cerebral blood flow, glucose carrying capacity also decreases in polycythemia. As a result plasma glucose concentration, especially venous one is lower than normal [9]. Hypocalcemia and hyperbilirubinemia may also be seen in
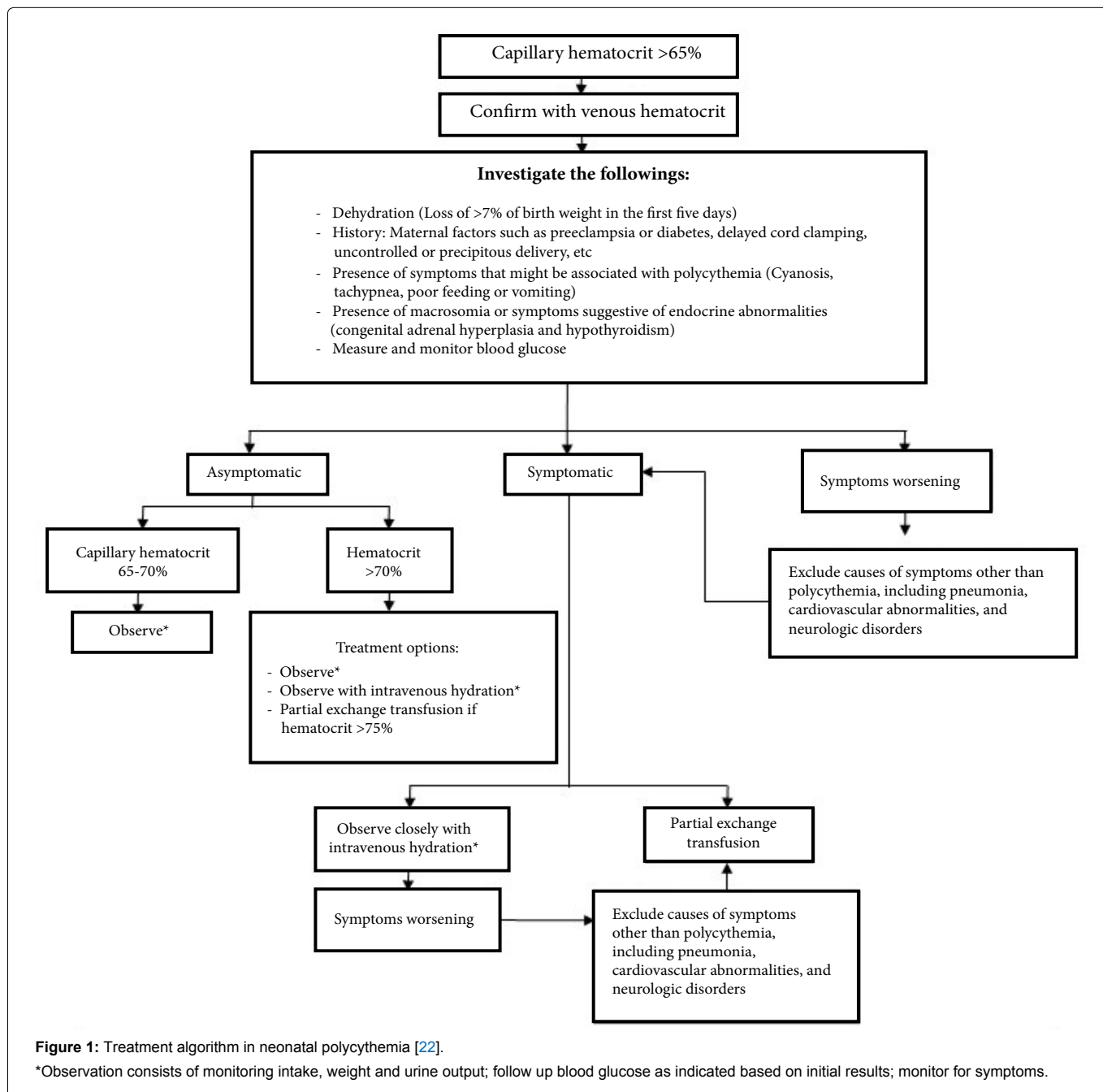

Figure 1: Treatment algorithm in neonatal polycythemia [22].

*Observation consists of monitoring intake, weight and urine output; follow up blood glucose as indicated based on initial results; monitor for symptoms.

polycythemic newborns [9,11]. The level of calcitonin gene related peptide (CGRP) has been shown to be high in polycythemic newborns. This peptide regulates vascular tonus stimulating vasodilatation and leads to hypocalcemia, and high levels of CGRP suggest its role in response to polycythemia [40].

Thrombocytopenia, low antithrombin III levels, and more rarely development of thrombosis are hematological problems encountered in polycythemia [9,11]. As the density of the erythrocytes increases they accumulate in the center of blood flow, and thrombocytes, which are lighter, migrate to periphery of the vascular wall (thrombocyte margination). This causes the number of thrombocytes to be counted lower than the actual count (relative thrombocytopenia) [7,32].

Is Routine Screening Necessary?

Screening is not necessary in asymptomatic conditions [12,22]. Screening may be considered in symptomatic cases and some selected high-risk groups (Small-for-gestational age and large-for-gestational age newborns, newborns of diabetic mothers, monochorionic twins) in the presence of symptoms suggestive of polycythemia. Capillary hematocrit measurement is the method of choice for screening.

Treatment

In clinical practice one of the most commonly encountered causes of polycythemia is dehydration. Therefore dehydration, which may develop secondary to causes such as fever, feeding problems, vomiting and diarrhea should be excluded before establishing a diagnosis of polycythemia [9]. Polycythemia due to dehydration may be present in a period extending into the 2-3 days of life in contrast to most of the early causes of polycythemia. Birth weights and actual weights of the babies should be compared, and dehydration should be suspected in case of weight loss over 7% in the first five days of life [22]. In case of dehydration, this situation should be corrected by increasing fluid intake, and hematocrit measurement should be repeated there after [9,11]. All polycythemic newborns should be investigated and followed for neurologic, gastrointestinal and cardiopulmonary signs and commonly encountered complications such as hypoglycemia and hyperbilirubinemia [9,11,22].

Treatment options in polycythemic patients depend on whether they are symptomatic or not and their hematocrit levels (Figure 1) [22].

Asymptomatic polycythemia

Treatment option in asymptomatic polycythemic patients depends on the hematocrit level (Plethora is not considered as a symptom).

Asymptomatic patients with a peripheral venous hematocrit level between 65-70% should be observed for intake, weight, and urine output providing sufficient hydration and glucose intake. Serum bilirubin and glucose levels should be checked when necessary. While monitoring for the development of symptoms, a venous hematocrit mesurement should be repeated in 12-24 hours. If the repeated hematocrit is below 70% and no symptoms develop, the same policy should be continued for 24 hours and a hematocrit measurement should be repeated.

For the patients with a peripheral venous hematocrit level above 70%, there are a few treatment options. Some clinicians prefer to continue observation with or without providing intravenous hydration. Some other clinicians prefer partial exchange transfusion (PET) in asymptomatic patients only if venous hematocrit is above 75% [41,42], whereas some others advise PET if venous hematocrit is above 70% even in asymptomatic cases (less common) [12,43,44].

Symptomatic polycythemia

The optimal management of symptomatic polycythemic newborns has not been exactly established and there are various approaches. Some clinicians perform PET to lower hematocrit in symptomatic cases with a peripheral venous hematocrit level above

65% [41]. Neonatal hematocrit and blood viscosity peaks between two and four hours after birth, and also considering that most of the studies reporting no favourable long-term benefits of PET on neurodevelopmental outcome have been performed PET after 6 hours of age, PET should be done as soon as possible (in the first 2-4 hours of life) after a decision is made to perform PET [12,22]. On the other hand some clinicians prefer close observation with intravenous hydration. The main aim of intravenous hydration is to prevent the development of hypoglycemia, a common complication of polycythemia. Intravenous fluid should be provided for the first 24 to 48 hours of age at a rate of at least 100 ml/kg per day, including glucose at a rate 6 to 8 mg/kg per min. With this approach a PET is performed only if there is worsening of symptoms, such as persistent hypoglycemia, or persistent cyanosis/apnea, or gastrointestinal symptoms [22].

PET treatment

Isovolumetric PET reduces hematocrit without causing hypovolemia. Although PET acutely demonstrates hemodynamic improvements in cerebral blood flow, cardiac index and oxygen transport [45-51], its long-term effects on psychomotor and neurodevelopmental outcome have not clearly been established and are under debate.

PET can be performed via peripheral or central routes. In peripheral route, peripheral arteries and veins are used. Blood is removed from an arterial catheter, and normal saline is simultaneously infused into a peripheral vein. In central route, blood is removed from an umbilical venous catheter and normal saline is simultaneously infused into a peripheral vein. Umbilical venous catheter also can be used for both removing blood and infusing fluid [11], and this method is the most commonly used method in practice.

The exchange volume is calculated using the following formula:

$$Exchange\ volume = \frac{\left(Observed\ hematocrit - Desired\ hematocrit^{*}\right) \times Blood\ volume^{**}}{Observed\ hematocrit}$$

*Desired hematocrit is usually 55%.

**Blood volume is 80-90 ml/kg in term babies and 90-100 ml/kg in preterm babies.

In general the exchange volume is 15-20 ml/kg [22].

Crystalloids such as normal saline or ringer's lactate or colloids such as fresh frozen plasma or 5% albumin can be used for PET. These two types of fluids provide a similar efficacy in lowering hematocrit [11], and normal saline is the fluid of choice to be used in PET since it does not carry the risk of transfusion associated infections, and less expensive and easily available [11,52].

Prognosis

In acute phase the incidence of seizures and intracerebral hemorrhages is higher in polycythemic babies in comparison to normal babies. The early neonatal behaviour of polycythemic babies assessed by Brazelton Behavioral Assessment Scale demonstrated abnormalities of hypotonia, poor state control and irritability [53]. The long-term neurodevelopmental outcome of polycythemic infants remains controversial. Malanand de V Heese (1980) reported no neurodevelopmental differences between polycythemic and normal infants on follow-up at 8 months of age [54]. Delaney-Black, et al. (1989) reported speec hand fine motor abnormalities in polycythemic infants at 2 years of age. In the same children at 7 years of age they noted lower spelling and arithmetic achievement test results and gross motor skills than normal control children [55].

Long-term effects of PET on neurodevelopmental outcome in comparison to conservative treatment have been studied in limited number of studies [30,44,48,53,54,56,57]. In none of these studies a positive effect of PET on long-term neurodevelopmental outcome could be demonstrated. Dempsey and Barrington (2006) have performed a systematic meta-analysis on five of these studies [30,48,53,54,56], and investigated whether PET has positive short-

term or long-term neurodevelopmental effects in polycythemic infants [37]. The authors reported no improvement in long-term neurologic outcome (mental developmental index, incidence of developmental delay, and incidence of neurologic diagnoses) after PET in symptomatic or asymptomatic newborns. There was also no improvement in early neurobehavioral assessment scores (Brazelton Neonatal Behavioral Assessment Scale) [37].

In another review, Ozek, et al. (2010) performed a meta-analysis on all of the 7 above-mentioned studies assessing the effect of PET on long-term neurodevelopmental prognosis [30,44,48,53,54,56,57], and evaluated the effect of PET especially on mortality and neurodevelopmental prognosis at 2 years of age and school-age [36]. Secondary parameters evaluated were seizures, cerebral infarct, necrotizing enterocolitis (NEC), hypoglycemia, hyperbilirubinemia, and thrombocytopenia [36]. Although the meta-analysis had limited data (poor follow-up) and did not account for patients who were lost on follow-up, the authors concluded that PET had no significant benefits in asymptomatic patients or those who have mild symptoms [36].

In addition to no documented positive effects of PET on long-term neurodevelopmental prognosis, and after the observation of a significant increase in the incidence of NEC in newborns performed PET [30,36,37,54], PET is currently being preferred in only (symptomatic) newborns who have symptoms associated with hyperviscosity and not in asymptomatic polycythemic newborns [8,12,22,36,37].

Criteria to Write the Review

Our main aim was to help pediatricians and neonatal caregivers who care for newborns to identify and manage those with neonatal polycythemia. On a monthly basis over the last 43 years, we have searched MEDLINE for English-language articles using the terms "neonatal polycythemia", "hyperviscosity", "partial exchange transfusion" and "hematocrit". We also reviewed articles on these subjects in the Cochrane Database of Systematic Reviews, as well as all meta-analyses and recent textbooks, all published from 1982 to 2016.

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Sarıcı et al. Clin Med Rev Case Rep 2016, 3:142

ISSN: 2378-3656   • Page 5 of 6 •

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Sarıcı et al. Clin Med Rev Case Rep 2016, 3:142

ISSN: 2378-3656 • Page 6 of 6 •