

REVIEW ARTICLE

Neonatal polycythaemia: critical review and a consensus statement of the Israeli Neonatology Association

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ABSTRACT

The aim of this paper is to critically review neonatal polycythaemia (NP) literature, in terms of definition, diagnosis and management. We reviewed all Medline articles on NP up to December 2009. (i) The textbook definition of NP [venous haematocrit (HCT) > 65%] is empirical and not based on statistical definition, symptoms or complications. (ii) Measurement of viscosity is not better than HCT in predicting complications. (iii) Normovolaemic NP because of increased erythropoiesis may be different from hypervolaemic polycythaemia because of excessive foetal transfusion. (iv) Coexisting hypoglycaemia may worsen long-term outcome. (v) Four clinical trials (CTs) studied partial exchange transfusion (PET) on outcomes. In all trials, PET was performed after 6 h of life. There is no evidence that PET improves neurodevelopmental outcome of asymptomatic NP, and it might increase the risk of necrotizing enterocolitis. These CTs have inherent design flaws: (a) CNS 'damage' may occur before PET. (b) Confounding variables that may affect outcome have not been studied. (vi) If PET is performed, normal saline is the best alternative. (vii) The long-term effect of PET on symptomatic infants has not been studied.

Conclusion: Current definition and management of NP are little evidence based, thus the need for a consensus based on expert opinion.

INTRODUCTION

The aim of this article is to produce a consensus statement about a highly controversial topic, that of neonatal polycythaemia (NP). Specifically, we will attempt to offer a more precise definition of polycythaemia and to review the multiple factors that potentially influence neonatal haematocrit (HCT). We will then address the issue of whether blood viscosity should or not be measured in polycythaemic infants, in order to make therapeutic decisions. We will review the major causes of polycythaemia, as well as its effects (signs and symptoms) and complications. We will summarize the major clinical trials that studied the effects of partial dilution exchange transfusion (PET) on outcome, as well as those that studied the technical aspects of PET (such as routes of exchange or fluids to be exchanged with blood). Finally, we will make specific recommendations both in terms of diagnosis and in terms of management of NP, once diagnosed. This position statement was distributed to and voted upon by all neonatologists in Israel (with a majority of more than 2/3 according to the regulations of the Israel Neonatal Society).

HOW DO WE DEFINE NP?

Neonatal polycythaemia is empirically defined in most neonatology textbooks as a venous HCT \geq 65% (1,2). This

number is not based upon a statistical definition of infants at risk, above a certain percentile or a certain number of standard deviations above the mean. It is neither based upon the risk for symptoms nor for complications and does not clearly discriminate between symptomatic and asymptomatic infants and between those who will or will not develop short- or long-term complications (3–5). Moreover, the presence of early symptoms may not allow discriminating between patients who will or will not develop long-term complications (5). It is unclear when exactly the venous HCT value of >65% emerged from the first time in the literature, but it was associated with the belief that at a venous

Key notes

- Neonatal polycythaemia (NP) is defined empirically as a venous HCT > 65%.
- In all four trials that studied partial exchange transfusion (PET) on outcomes, PET was done after the age of 6 h, i.e. after the post-natal peak in HCT, did not improve neurodevelopmental outcome of asymptomatic NP, and might have increased the risk of necrotizing enterocolitis.
- The long-term effect of PET on symptomatic infants has not been studied.

HCT value of '60–70%' the blood viscosity 'started' to increase in an exponential manner, an inaccurate concept because it has been shown that the relationship between HCT and blood viscosity is exponential at *all values* studied of HCT (4).

Furthermore, many factors influence normal HCT and their knowledge is fundamental in order to understand the empirical aspect of the currently accepted definition. These factors are the gestational age of the infant, the degree of placental transfusion, the site of blood sampling and the time of blood sampling.

Gestational age

Haematocrit increases progressively with increasing gestational age (1–3); thus, NP may occur at much higher rates in post-term than in preterm infants (6). Consequently, epidemiologic studies of NP must take into account the length of gestation.

Degree of placental transfusion

At term, the total foetoplacental blood volume is about 115 mL/kg foetal weight and is distributed in the 'normal' full-term infant after birth as approximately 70 mL/kg in the infant, with 45 mL/kg remaining in the placenta (7). This distribution may vary considerably, as more or less blood may remain in the placenta. The main factors influencing placental transfusion are time of cord clamping, position of the delivered infant in relation to the placenta, onset of respiration, presence or not of intrauterine hypoxia and presence or not of cord compression (8).

1. *Time of cord clamping.* Within 30–45 s following birth, the umbilical arteries are functionally closed, while blood flow from placenta to foetus through the umbilical vein may continue for a few additional minutes (9). When the infant is delivered at or below the introitus level, if the cord is not clamped, her/his blood volume will increase in a stepwise manner, reaching 55% additional volume after 3 min (9).
2. *Position of the delivered infant in relation to the placenta.* In vaginally delivered infants who are kept 50–60 cm above the placenta, placental transfusion does not occur (7). In contrast, if they are maintained 40 cm below the placenta, placental transfusion is hastened (7). Infants born by caesarean section are more likely, if cord clamping is delayed, to have a lesser blood volume than infants born vaginally (10,11). In a recent study, it was demonstrated that the onset of labour might start the process of placental transfusion within the womb, as cord blood HCT of infants delivered vaginally is lower than that of infants delivered by elective caesarean sections without labour (12).
3. *Onset of respiration.* This point is controversial, as onset of respiration (through generating a negative intrathoracic pressure and presumably increasing the placental–foetal transfusion process) has been found to have little (13), or not effect (11) upon blood volume at birth.

4. *Presence or not of intrauterine hypoxia.* Acute intrapartum and intrauterine asphyxia can be accompanied by an increase in HCT (presumably through increased transcapillary escape of plasma) (14). In addition, changes in umbilical blood flow and in placental vascular resistance may theoretically affect the distribution of blood between the foetus and the placenta.
5. *Presence or not of cord compression.* Presumably, because the umbilical vein is more compressible than the umbilical arteries, infants born with a tight nuchal cord may actually have low blood volume at birth (15).

Site of blood sampling

Capillary HCT is generally higher than venous HCT (16) which in turn is higher than 'central' HCT (from umbilical vein) (17). Capillary HCT from warmed heels correlates well with venous HCT (18), but there is only a loose correlation between capillary blood from unwarmed heel sticks and umbilical vein HCT (16).

Time of blood sampling

Haematocrit rises from values obtained at birth (from cord venous or arterial sampling) to reach a peak at 2 h of age, staying at a plateau for 2 additional hours, and then decreases to go back to values close to cord blood values by 12–18 h of age (3,4,17).

Screening programs for NP will therefore be strikingly affected by the time of sampling: the rate of 'NP' (venous HCT $\geq 65\%$) in 'normal newborns' is as high as 20% (if screening is effected at 2 h of age) and as low as 2% (if screening is effected at 12–18 h of age) (3,4,17).

SHOULD WE MEASURE HAEMATOCRIT OR BLOOD VISCOSITY?

The following questions must be addressed: (i) can we define hyperviscosity? (ii) how is viscosity related to HCT? and (iii) are symptoms and/or complications of polycythaemia related to hyperviscosity?

Can we define hyperviscosity?

Blood viscosity is measured using a microviscometer and expressed in centipoise at various sheer rates. Published 'normative' data differ by several important variables such as time of sampling, site of sampling and cord clamping time. Traditionally, most authors have defined hyperviscosity using the criteria developed by Gross et al. (18) who used two standard deviations above the mean obtained in *cord blood* from normal infants. These values may actually lead to an overestimation of hyperviscosity, in particular when HCT and viscosity are measured at 2–6 h of life. It is difficult to choose a specific number of viscosity above which infants are definitely 'hyperviscous' and below which they are 'normal.' At the present time, any definition of hyperviscosity would be a statistical one; the choice of the second standard deviation above the mean would imply that by definition, 2.5% of a *normal* population of

Table 1 Symptoms and other findings associated with neonatal polycythaemia

'Feeding problems'
Plethora
Cyanosis
Lethargy
Hypotonia
Respiratory distress
Jitteriness
Hypoglycaemia
Hyperbilirubinaemia

newborns would be considered as hyperviscous. This statistical definition would identify *at risk*, rather than a *dis-eased* population.

How is viscosity related to HCT?

Viscosity and HCT correlate exponentially (4). The post-natal increase in HCT is accompanied by a similar increase in viscosity. (3,4,18). In neonates, the major determinant of total blood viscosity is HCT, with plasma viscosity playing a minor role (19,20).

Are symptoms and/or complications of NP related to hyperviscosity?

Many symptoms have been described as linked to polycythaemia. In general, they are not specific and are shared by many neonatal conditions such as, for instance, sepsis, asphyxia, hypocalcaemia, hypoglycaemia, respiratory or cardiovascular disorders. Table 1, extracted from Wiswell et al.'s work (21), states the frequency of symptoms and complications associated with polycythaemia (PCT) in 932 infants delivered in military hospitals. Importantly, there is no control group that allows determining whether these symptoms and complications are truly or not linked to PCT.

No study has shown a correlation between signs and symptoms, or complications of NP to the actual value of blood viscosity. Measurement of viscosity has not proven to be superior to that of HCT in identifying newborns at risk for short- or long-term complications.

CAUSES OF POLYCYTHAEMIA

Neonatal polycythaemia may be classified as normovolaemic, hypervolaemic or hypovolaemic.

Normovolaemic polycythaemia

Normovolaemic polycythaemia in the newborn refers to the condition where normal intravascular volume is present despite an increase in red cell mass. It results from increased RBC production because of placental insufficiency and/or chronic intrauterine hypoxia, such as found in intrauterine growth restriction (22), maternal pregnancy-induced hypertension (22), discordant twins (23), maternal diabetes mellitus (24,25), prolonged intrauterine tobacco exposure, active (26) or passive (27), and post-maturity (28).

Hypervolaemic polycythaemia

Hypervolaemic polycythaemia occurs when higher than average blood volume is accompanied by an increased red cell mass. Hypervolaemic polycythaemia usually occurs in cases of acute transfusion to the foetus such as maternal-foetal transfusion (29), twin-to-twin transfusion (30) and also within the broad category of placental transfusion as mentioned previously.

Hypovolaemic polycythaemia

Hypovolaemic polycythaemia occurs secondary to a relative increase in number of erythrocytes to plasma volume (31). This condition usually results from intravascular dehydration and can be remedied by adequate rehydration (31).

EFFECTS AND COMPLICATIONS OF POLYCYTHAEMIA

Pathophysiology

Theoretically, polycythaemia may lead to symptoms and/or complications through hyperviscosity, decreased organ blood flow, increased cellular breakdown of the increased red cell mass and through the haemodynamic effects of hypervolaemia or of hypovolaemia.

1. *Hyperviscosity*. Experimental isovolaemic NP leads to a reduction in cerebral blood flow (CBF) (32). Decreased CBF in experimental NP is compensatory to the increased O₂ content rather than a consequence of hyperviscosity (32). However, theoretically, decreased blood flow to the brain may lead to a decrease supply to the brain of other substances carried by plasma, such as glucose and amino acids.
2. *Decreased cerebral blood flow*. In experimental polycythaemia, glucose delivery and utilization in the brain decreases (33). Moreover, an experimental increase in whole-blood viscosity through infusion of concentrated cryoprecipitate, in spite of constancy of red cell mass and O₂ content, leads to a reduction in CBF (34).
3. *Increased cellular breakdown of the increased red cell mass*. Increased breakdown of red cells in NP may be a significant contributing factor of neonatal hyperbilirubinaemia (24).
4. *Haemodynamic effects of hypervolaemia or of hypovolaemia*. Such haemodynamic effects are applicable to conditions of hypervolaemic and hypovolaemic polycythaemia and cannot be fully addressed in the context of these guidelines. Briefly however, hypervolaemia may lead to congestive heart failure, pulmonary oedema and cardiorespiratory failure (35). In contrast, hypovolaemia can lead to hypoxic-ischaemic injury to vital organs.

Neurological complications

Jitteriness and irritability have been noted in polycythaemic infants during the immediate newborn period. Seizures and intracerebral haemorrhages have also been reported.

Multiple cerebral infarcts have also been noted in patients with polycythaemia (20).

The early neonatal behaviour of polycythaemic infants may also be affected, as shown by Goldberg et al. (36) who found abnormalities in the Brazelton Behavioral Assessment Scale in polycythaemic infants as compared to controls. Specific abnormalities noted included hypotonia, poor state control and irritability (36).

The long-term neurodevelopmental outcome of polycythaemic infants remains controversial. Malan and de V Heese (37) found no neurodevelopmental differences between hyperviscous and normal infants upon follow-up at 8 months of age. Most studies report that polycythaemic infants are at higher risk for development delays than controls upon follow-up (5,38). Speech and fine motor abnormalities were noted in polycythaemic infants at 2 years. Upon follow-up of polycythaemic infants at 7 years of age, they were noted to have lower spelling and arithmetic achievement test results and gross motor skills than control, non-polycythaemic infants (38). However, most publications that studied the long-term effects of partial exchange transfusion (PET) on neurodevelopmental outcome did not show that the procedure affected the outcome in any spectacular manner, as will be discussed later.

Effect on cardiac function

Experimental polycythaemia increases coronary vascular resistance in dogs (39). In neonates with polycythaemia, there is an increase in pulmonary and systemic resistances that may lead to significant myocardial dysfunction and a decrease in shortening fraction (40).

Hypocalcaemia and hypomagnesaemia

A prospective study of 49 polycythaemic infants revealed that 30% had hypomagnesaemia [serum Mg < 0.62 mmol/L (1.5 mg/dL)] and 8% had hypocalcaemia [serum Ca < 4 mmol/L (8 mg/dL)] (37). Daily serum measurement of Ca and Mg in 9 of 10 infants who underwent exchange for polycythaemia was quoted as normal (38). In infants of diabetic mothers, the rates of hypocalcaemia and hypomagnesaemia do not appear to be different in polycythaemic or non-polycythaemic infants, a finding that does not support the theory of a causal relationship between these neonatal complications (25).

Hypoglycaemia

In experimental polycythaemia, hypoglycaemia occurs within hours and is not accompanied by elevated blood insulin concentrations (33). It may be because of increased glucose consumption by the increased red cell mass or because of reduced plasma volume ('reduced glucose-carrying capacity') but the exact mechanism is unclear (33). Hypoglycaemia may be prolonged, severe and in one case report persisted until exchange transfusion was undertaken (41). However, in many cases, hypoglycaemia will coexist with polycythaemia without clear proof that the two are causally related, such as in infants of diabetic mothers (24), in small for gestational age (SGA) infants (42) or in

asphyxiated patients (4). Nevertheless, in a non-randomized trial, infants with coexisting polycythaemia and hypoglycaemia had the worst long-term outcomes (4).

Thrombocytopenia

Thrombocytopenia may theoretically result from platelet consumption because of intravascular coagulation or may reflect diversion of stem cell haematopoiesis to increase RBC mass from increased erythropoietin production (22). It is unclear whether thrombocytopenia and polycythaemia are causally related. They tend to coexist in situations of chronic intrauterine hypoxaemia where a shift of multipotent stem cell to erythropoiesis at the expense of thrombopoiesis may occur, such as in SGA infants (22) or in infant of diabetic mothers (IDMs) (24).

Hyperbilirubinaemia

As mentioned earlier, the hyperbilirubinaemia frequently observed in polycythaemic infants is probably due, in part to the breakdown of the increased RBC mass (43). Alternatively, it is also possible that the increased erythropoiesis rate that led to normovolaemic polycythaemia was accompanied by an excessive rate of ineffective erythropoiesis (24).

Necrotizing enterocolitis

This will be discussed later.

EFFECTS OF PARTIAL DILUTIONAL EXCHANGE TRANSFUSION (PET) ON OUTCOME

The relationship between PET and its effects on outcome relies upon three possible theories: According to the first one, PCT, through hyperviscosity and/or other mechanisms, may lead to significant complications. If this is true, dilutional exchange transfusion affected in a timely fashion should greatly reduce the rate and gravity of these complications. According to the second one, the traditional complications of polycythaemia are actually not because of polycythaemia itself, but are because of another mechanism (e.g. chronic intrauterine hypoxia) which also led to polycythaemia. If this is true, dilutional exchange transfusion should affect neither the rate nor the severity of these complications. According to the third one, a common mechanism (e.g. chronic intrauterine hypoxia) leads to both polycythaemia and other complications, but polycythaemia also contributes to or aggravates these complications; if the latter theory is true, dilutional exchange transfusion should only partially reduce the rate and gravity of these complications.

Four clinical trials of PET in NP have been conducted, in attempt to determine the effect of PET on various short- or long-term outcomes. These are the studies by Malan and de V Heese (37), Goldberg et al. (36), Black et al. (38,44,45) and Bada et al. (46).

In Malan and de V Heese's study (37), 49 neonates selected by presenting with the clinical 'appearance' of PCT, a venous HCT > 65 and who had no or mild symptoms were randomized to PET or symptomatic care. PET was

performed at >12 h in all infants. Patients were followed up at 8 months of age. Eighty-six per cent of them were examined at follow-up, and 14% were lost to follow-up. There was one death from necrotizing enterocolitis (NEC) in the treatment group. There were 'no differences' in developmental score and no differences in neurological examination, which was normal in all infants of both groups (37).

In Goldberg et al.'s 1982 study (36), 20 neonates were selected by a screening capillary HCT > 68% and the presence of hyperviscosity on venous blood (using Gross' criteria). They all were asymptomatic neurologically. Patients were randomized to PET or symptomatic care. PET was performed at >12 h in all infants. The follow-up visit was performed at 8 months of age. Eighty per cent of the patients were examined (20% were lost from follow-up). Bayley motor developmental index (MDI) and psychomotor developmental index (PDI) performed at the follow-up visit were not significantly different between the two groups. There also were no differences in neurological findings (abnormal in six of 10 infants in the treatment group and zero of six in the control group). Of note, Brazelton scores were immediately improved by PET (36).

In Black et al.'s study (38,44,45), 93 neonates were selected by admission to the nursery at 4–6 h, a heel stick screening HCT > 65%, a repeat venous HCT > 65% and a venous blood viscosity increased (using Gross' criteria). Both symptomatic and asymptomatic infants were eligible for the study. They were randomized to PET or symptomatic care. PET was performed at 8–12 h of age (44,45). Systematic follow-up was initially conducted at 2 years of age (44). There was only a 65% follow-up rate. Results were as follows: the mental delay rate was non-significantly reduced by PET (13% vs. 18%). The motor delay rate was reduced by PET (19% vs. 35%) in a non-significant manner. When mental and motor delay rates were combined, the 'neurological diagnosis' rate was significantly reduced by PET (25% vs. 55%) ($p < 0.05$) (45). However, eight hyperviscous patients treated with PET, and no control infants developed typical NEC (blood in the stools, pneumatosis and systemic signs) ($p < 0.01$) (45). The authors of this study were able to conduct an additional follow-up encounter at school age (7 years) in 93 children (43 polycythaemic and 40 non-polycythaemic control infants) (38). Although both polycythaemic subgroups did poorer than the control infants, there was no difference between exchanged and non-exchanged patients in terms of intelligence quotients, or scores on the wide range achievement test (38).

Bada et al.'s study, reported in 1992 (46), included 28 neonates, selected by a cord blood screening HCT > 57, an arterial blood HCT > 62% and the presence of hyperviscosity (using Gross' criteria); only asymptomatic infants were retained and were randomized to PET or symptomatic care. PET was performed at >6 h (average 10 h). The follow-up was conducted at >24 months (mean 27.5 months). There was a 71% follow-up rate. There were no significant differences in MDI/intelligence quotient (IQ) between the groups (mean score 85 in the treated group versus 88 in controls). The 'borderline' mental retardation rate was even

higher in the treated group than in the control group (66% vs. 45%) (46).

Thus, from the above-mentioned studies, there is no evidence that PET alters the neurological or developmental outcomes of asymptomatic polycythaemic neonates. This is also the conclusion of the systematic review conducted by Dempsey and Barrington (47). There is even evidence that PET might increase the risk of NEC in polycythaemic neonates (45,47). However, it is possible that something related to the way the procedure was conducted may have increased the risk of developing NEC. Indeed, in all above-mentioned clinical trials, PET was performed while using umbilical vein catheterization and by withdrawing blood then infusing the diluting fluid repetitively. Hein and Lothrop (48) reported that, when isovolaemic exchange transfusion was performed, i.e. when blood withdrawal and fluid infusion were conducted simultaneously, there was no evidence of severe gastrointestinal injury in any of 185 infants.

We do believe, however, that the clinical trials conducted to date do not allow to reach a practical conclusion, because of the following inherent flaws in design: (i) CNS 'damage' may have already occurred before PET was conducted, because PET was performed too late (after the peak and plateau of HCT and viscosity); (ii) confounding variables that may have affected the outcome (such as number of IDMs, infants of pre-eclamptic mothers, smokers, intra-uterine growth restriction (IUGR), in whom CNS 'damage' may have occurred *in utero*, unrelated to the polycythaemia), were not taken into account in any study; (iii) the small sample size of all studies is likely to have conferred a large type-2 error; (iv) follow-up of infants was very partial and did not included all of them. Thus, this working group concludes that PET performed after 6 h of life (after the peak HCT/viscosity) is not likely to significantly alter the neurological or developmental outcomes of asymptomatic polycythaemic neonates. Whether or not PET performed earlier than 6 h of life in asymptomatic infants improves long-term outcome is not known at the present time. Moreover, the effect of PET in symptomatic infants has not been systematically studied. On the short term, there is an improvement of cerebral functioning following PET, as demonstrated by an improvement in Brazelton scores (36), or in cerebral haemodynamics (49). The long-term effect of PET on such infants is unknown.

TECHNICAL ASPECTS OF PET

Which diluting fluid should be used?

The systematic review of the optimal fluid for exchange transfusion in NP reported by de Waal et al. (50) reviewed the studies of Tapia et al. (51) comparing plasma to albumin and to normal saline (NS), Deorari et al. (52), comparing plasma to NS, Roithmaier et al. (53) comparing plasma to Ringer lactate, Wong et al. (54) comparing albumin to NS, Krishnan and Rahim (55) comparing plasma to NS, and Jan et al. (56) comparing plasma to NS. This systematic review concluded that PET is efficient in relieving immediate

symptoms and reducing HCT. It did not find however that there were clinically important differences among plasma, 5% albumin, NS or Ringer solution when used in PET in reducing HCT. Thus, NS is the optimal fluid (cheapest, with less potential side-effects).

How much to exchange?

Neonatology textbooks universally recommend (1,2), whenever PET is effected, to aim for a target, post-PET HCT of 55% (1). Thus, the formula used for exchange transfusion is (in ml): $(\text{HCT}-55) \times \text{W} \times 80/\text{HCT}$ (where HCT is the pre-PET HCT and W is the infant's weight in Kg) (1).

CONCLUSIONS

1. PCT is a venous HCT of at least 65%. Such a number is much more likely to be significant in an infant >6 h than it is at 2–4 h of age.
2. Symptoms/complications of polycythaemia are unlikely to be related to a HCT of <65%.
3. The need for PET and its efficacy have not been demonstrated when PET was conducted after 6 h of life in asymptomatic infants (regardless of their HCT). There is no evidence that PET alters the neurological or developmental outcomes of asymptomatic polycythaemic neonates. Moreover, it is not known whether prematurity affects or modifies any of our conclusions from this critical review of the literature.

RECOMMENDATIONS

1. Routine screening for polycythaemia is not recommended.
2. Routine performance of PET in asymptomatic infants is not recommended.
3. Screening for symptoms should be performed carefully and documented in all infants with polycythaemia.
4. Normality of blood glucose should be documented in all infants found to have polycythaemia.
5. PET causes a prompt relief of symptoms. Thus, according to most authors, the presence of symptoms (or of hypoglycaemia) should lead to perform PET. From a medicolegal standpoint, it appears impractical to perform PET within 6 h from birth, and in the vast majority of cases, if PET is performed, it will be effected after the peak HCT and viscosity have already occurred. Recognition of symptoms, capillary measurement confirmed by venous sample, explanation and consent from the parents will in our opinion take more than 4–6 h in the vast majority of cases.
6. PET should be performed as early as possible whenever symptoms are present, in view of the potential for more severe symptoms and complications to develop. Before proceeding with PET, it appears that there is a

need for thorough, timely, clinical and physical assessment of the newborn.

7. If performed, PET should be done with normal saline.

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