Short and longterm outcomes following partial exchange transfusion in the polycythemic newborn: A systematic review

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Keywords: polycythemia, partial exchange transfusion, neurodevelopmental outcome
Abstract

**Background:** Severe polycythemia in the neonate may produce symptoms due to hyperviscosity and may be associated with serious complications. Partial Exchange Transfusion will reduce the haematocrit.

**Objective:** To determine whether partial exchange transfusion in term infants with polycythemia (symptomatic and asymptomatic) is associated with improved short term and long term outcomes.

**Search Strategy:** We searched Medline, EMBASE and the Cochrane Controlled Trials Register of the Cochrane Library. The following keywords were used: polycythemia, partial exchange transfusion, hyperviscosity, and limited to the newborn. This covered years from 1966 to 2004. We also searched abstracts of the Pediatric Academic Societies and personal files.

**Selection Criteria:** Randomized or quasi-randomized trials in term infants with polycythemia and/or documented hyperviscosity were considered. Clinically relevant outcomes included were short-term (resolution of symptoms, neurobehavioural scores, major complications) and long-term neurodevelopmental outcome.

**Data Collection and Analysis:** We extracted, assessed and coded separately all data for each study. Any disagreements were resolved by discussion.

**Main Results:** 6 studies were identified; five had data that could be evaluated for analysis. There is no evidence of an improvement in long-term neurological outcome (Mental Developmental Index, incidence of mental delay and incidence of neurological diagnoses) following partial exchange transfusion in symptomatic or asymptomatic infants. There is no evidence of improvement in early neurobehavioural assessment scores (Brazelton Neonatal Behavioural Assessment Scale). Partial exchange transfusion may be associated with an earlier improvement in symptoms, but there are insufficient data to calculate the size of the effect. Necrotizing enterocolitis is probably increased by partial exchange transfusion (RR 8.68, 95% CI 1.06, 71.1)

**Conclusion:** There is no evidence of long-term benefit from partial exchange in polycythemic infants and the frequency of gastrointestinal injury is increased. The long-term outcome is more likely to be related to the underlying cause of polycythemia.
Introduction

Polycythemia occurs in 2-5% of term newborns, usually occurring as a compensatory mechanism secondary to intrauterine fetal hypoxia, or sometimes as a result of delayed cord clamping. Polycythemia leads to hyperviscosity, which can result in impaired end organ perfusion; this can manifest as neurological, cardiorespiratory, gastrointestinal, and metabolic symptoms. These symptoms are generally transient and may be minor despite severe degrees of polycythemia. Although serious complications such as renal vein thrombosis or cerebral venous sinus thrombosis have been described in infants with polycythemia, these are rare, and the principle clinical concern is that polycythemia may be associated with adverse long-term neurological sequelae.

Partial exchange transfusion (PET) has been used as a therapeutic modality to reduce Hct and thereby blood viscosity while at the same time maintaining intravascular volume. Observational studies suggest that symptomatic infants who undergo PET may have an improvement in symptoms; however, the symptoms are in any case transient. More importantly, it is also unclear if PET is associated with improved long-term neurological outcome. The objective of this systematic review was to assess the efficacy and safety of PET in the treatment of the polycythemic newborn.

Methods

Criteria for inclusion

Studies were included if they were randomised or quasi-randomized clinical trials; if the participants were newborns with documented central polycythemia, defined as a central haematocrit greater than or equal to 64%; and if the interventions consisted of a PET designed to reduce central Hct to 60% or less, compared to observation only.

Outcome measures

1. Long term neurodevelopmental, expressed as the proportion of infants with a neurologic diagnosis, proportion with developmental delay and/or with motor abnormalities at 18 months or greater. Alternatively, evaluation of cognitive or motor development using a validated continuous scale was acceptable.
2. Short term clinical neurological assessed by neurological and behavioural assessment scores
3. Short term clinical as determined by resolution of symptoms attributed to polycythemia.
4. Adverse events.

Search strategy for identification of studies

The search was performed using the MEDLINE (1966 - 2005), EMBASE (1986 - 2005) and the Cochrane Register of Controlled Trials. Keywords used were; polycythemia, partial exchange transfusion, hyperviscosity and limited to newborn. Abstracts from the Society for Pediatric Research were also reviewed. The search revealed 94 reports: each
was inspected to determine their suitability for inclusion. Original papers were retrieved and reviewed. Citations from these papers were also assessed.

Each identified trial was assessed for methodological quality with respect to (i) clear statement of inclusion and exclusion criteria (ii) reliability of the method of randomization including generation of randomisation sequence and masking of allocation (iii) masking of treatment groups at follow up (iv) completeness of follow up. We felt that masking of the intervention was not feasible. Where deemed appropriate meta-analysis was performed using Revman 4.2 software utilising a random effects model. For dichotomous outcomes we calculated a relative risk and 95% confidence intervals, and for continuous variables a weighted mean difference and 95% confidence interval. Heterogeneity was evaluated using the $I^2$ statistic.

Results

We identified a total of five randomized controlled trials of PET in newborns with polycythemia or hyperviscosity (Van der Eelst, Goldberg, Black, Bada and Ratrisawadi). A sixth study, published in abstract form by Hakanson was excluded due to inadequate data availability. Table 1 provides a description of the included studies and Table 2 the methodological quality of each study.

Analysis of outcomes

Neurodevelopmental Assessment at 18 months or greater

Mental delay was assessed in 2 studies. Bada presents both the mean scores and the number with “suspect/borderline mental retardation”, (precise definition is not given). Black presents the proportion of infants with “mental delay” (not further defined). The summary estimate of the RR for the presence of developmental delay was 1.26 (95% CI 0.62, 2.56) see figure 1. Ratrisawadi’s quasi randomized study had only 38% follow up at 2 years, abnormal DQ (Developmental Quotient) was defined as less than 100 on the Gasel developmental test, present in 11/25 of infants treated with PET and 4/15 controls. This study had a lower quality assessment (based on method of allocation and low follow up rate). However, performing a sensitivity analysis including this study does not change the conclusion of no benefit on proportion with neurodevelopmental delay at $\geq 18$ months (RR 1.36, 95% CI 0.78, 2.41). At 7 years of age there was no difference between the groups in terms of IQ or scores on the Wide range achievement test.

The mean difference (95% CI) for Mental Developmental Index (MDI) in the Bada study was -3.0 (-12.67, 6.67). The presence of a neurological diagnosis was assessed in 2 studies; the summary estimate of the RR is 0.73 (95% CI 0.13-4.18) see figure 2. There is moderate heterogeneity for this outcome, $I^2 = 40.5%$

Short term neurobehavioural assessment.

Three studies present data on short term neurobehavioural outcome assessed by the Brazelton Neonatal Behaviour Assessment Scale (BNBAS) and the Prechtl Scale. Van der Elst found no difference between exchanged and observed groups in BNBAS and
Prechtl scores at 10 days. Goldberg\textsuperscript{11} found a significant decrease in abnormalities initially present on BNBAS assessment when re-examined at 2 weeks only in the exchanged patients. Black mentioned that BNBAS was performed but no data are presented. These studies do not allow us to make any firm conclusions as to the short-term neurobehavioural effects of PET.

**Short-term symptoms**

The majority of infants in these studies are asymptomatic. Van der Elst\textsuperscript{10} presents data on clinical signs and noted that peripheral cyanosis improved in all 6 patients, 5 following PET and one spontaneously in the observation group. Bada\textsuperscript{13} noted clinical manifestations in the symptomatic polycytemic group resolved (87\%) or became less severe (13\%) after PET and Black\textsuperscript{12} noted that GI symptoms were common after PET. There is inadequate firm data to reach a conclusion.

**Adverse events**

Van der Elst\textsuperscript{10} noted 1 of 24 patients developed necrotizing enterocolitis (NEC) 24 hrs post exchange and required surgery, none of the 25 control patients developed NEC; there were no deaths. Black\textsuperscript{12} noted the onset of gastrointestinal symptoms in 42\% of patients following PET and in only 2\% of the controls, and note in a separate publication that 8 of the 43 PET infants developed typical NEC with pneumatosis and clinical symptoms, and none of the 50 controls\textsuperscript{5}. No adverse events were recorded in the Goldberg\textsuperscript{11}, Bada\textsuperscript{13} or Ratrisawadi\textsuperscript{14} studies. The relative risk for the development of NEC is 8.68 (95\% CI 1.06, 71.1).

**Discussion**

The current standard neonatal practice for performing a PET is (i) symptomatic with a Hct of 65\% or more\textsuperscript{17} (ii) asymptomatic with a haematocrit of 70\% or more. The Committee of the Fetus and Newborn of the American Academy of Pediatrics do not issue any definitive guidelines; stating that the accepted treatment of polycythemia is PET\textsuperscript{18}. We identified five randomized trials of PET in polycytemic newborns. Each study has small numbers of patients, utilise variable definitions of polycythemia based on Hct and have variable follow up times. Only two studies evaluated the efficacy of partial exchange in studies limited to asymptomatic patients\textsuperscript{13, 14}, both utilising a haematocrit of 65\% or more.

There are no randomized trials of PET in only symptomatic patients, which reduces the power of this review to determine the effects of PET in such infants. This lack of information is not surprising as there is a tendency to treat all symptomatic patients with PET, probably because of published recommendations\textsuperscript{17}. However, there appears to be no clear evidence that the long-term outcome of polycytemic infants is worse in symptomatic patients, compared to those who were asymptomatic. Bada\textsuperscript{13} evaluated the long term outcome of the 10 non-randomized symptomatic infants in her study, which do not appear to be substantially different to the outcomes of the asymptomatic infants in the randomized trial, the Bayley MDI for example was almost identical (90 +/- 13 in the symptomatic infants compared to 85 +/- 9 in the PET group and 88 +/- 13 in the
controls). Observational studies suggest that symptoms attributed to polycythemia do improve following PET\textsuperscript{19, 20} but these are in any case transient and the lack of controls prevents us from drawing any firm conclusions concerning the effect of PET on timing of resolution of symptoms. None of those studies that included both symptomatic and asymptomatic infants provided long term follow up information based on symptomatology. In particular patients with severe neurologic symptomatology (such as seizures) have not been reported separately, thus a possibility remains that such infants could have a long-term benefit. This, however, has not been demonstrated, highlighting the fact that there is no reliable evidence to support current practice.

The study by Bada\textsuperscript{13} of asymptomatic infants assessed at 24months or greater was unable to show any effect of PET on longterm neurodevelopmental outcome. We combined the findings of this study with the much larger study of Black\textsuperscript{12} (including both symptomatic and asymptomatic infants) and still found no neurological benefit. Even follow up to 7 years did not reveal any significant differences between the groups. These data would seem to indicate that probably the cause of the impaired long-term outcome is the cause of the polycythemia, most commonly intrauterine fetal hypoxia. Bada, for example, was unable to find an effect of PET, but noted on multiple regression analysis that fetal distress, hypoglycaemia and maternal pre-eclampsia were associated with poor outcome.

Although not a planned part of our analysis, data on medium term outcomes (8 months of age) were recorded in two studies\textsuperscript{10, 11}. Van der Elst\textsuperscript{10} reported that all infants followed to 8 months were neurologically normal and had “a developmental score appropriate for their age”. Goldberg\textsuperscript{11} examined 10 PET treated and 6 control infants and found 5/10 compared to 4/6 had abnormal neurological findings and almost identical Bayley scores. These studies included symptomatic and asymptomatic infants. Although developmental testing at such an early age does not accurately predict later functioning, these results support the findings of the planned analyses that no clinically important advantage is gained from PET.

PET is not without complications; in the 2 studies that report NEC, 9/67 PET infants, compared with 0/75 controls developed this disorder. In both studies PET was performed via umbilical catheterisation. These data suggest a temporal and causative relationship between NEC and umbilical PET. Thus the only apparent effect of PET from our analysis is an adverse outcome; however, many of the studies did not report the incidence of NEC, and the confidence intervals for this effect are very wide.

In conclusion we could not find reliable evidence that there is a clinically important benefit from PET in infants with polycythemia. There is, specifically, no evidence of a long term neurological benefit. Although the outcome of polycytheic infants is poorer than that of concurrently enrolled infants without polycythemia\textsuperscript{11, 13}, this is most likely related to the underlying cause of polycythemia, and is not improved by PET. It remains possible that infants with severe neurological symptoms could benefit from PET, as the literature does not appear to have enough power to eliminate such a benefit, however for infants with no symptoms or only minor symptoms, such as the majority of infants enrolled in these studies, the clinical decision of whether to intervene with PET should
take into account the lack of demonstrated benefit and the apparent increase in necrotizing enterocolitis.

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Competing interests
We have no competing interests to declare.

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Figure legends

Figure 1
Forest plot of effect of partial exchange transfusion in polycythaemic newborn infants on the proportion of infants with developmental delay at 24 to 30 months of age.

Figure 2
Forest plot of effect of partial exchange transfusion in polycythaemic newborn infants on the proportion of infants with a neurological diagnosis at 24 to 30 months of age.
References

<table>
<thead>
<tr>
<th>Study</th>
<th>Gestation</th>
<th>Sample size</th>
<th>Symptomatic/asymptomatic</th>
<th>HCT</th>
<th>Planned reduction</th>
<th>Mode of exchange</th>
<th>Short term Follow up Assessment</th>
<th>Longterm Follow up Assessment</th>
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<tbody>
<tr>
<td>Van der Elst:</td>
<td>Not clearly stated</td>
<td>49</td>
<td>No distinction made between symptomatic / asymptomatic. All symptoms considered minor</td>
<td>Central venous Hct of 65%</td>
<td>20-30mls/kg. Hct to &lt; 60%</td>
<td>Umbilical vein catheter FFP</td>
<td>BNBAS and neurological assessment of Prechtl at 10 d.</td>
<td>Neurological, developmental assessment at 8 months (similar to the Griffith Development Score)</td>
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<td>Goldberg</td>
<td>Not clearly stated</td>
<td>20</td>
<td>No distinction made between symptomatic and asymptomatic</td>
<td>Venous Hct ≥ 64% and hyperviscous Antecubital vein</td>
<td>Hct to 50% Based on Blood volume of 85mls/kg.</td>
<td>Umbilical vein catheter FFP</td>
<td>BNBAS at 8 hrs, 24 hrs, 72hrs and 2 weeks.</td>
<td>BSID and neurological assessment at 8 months</td>
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<tr>
<td>Black</td>
<td>“Term”</td>
<td>93</td>
<td>No distinction made between symptomatic and asymptomatic</td>
<td>Venous HCT 65% or more and hyperviscous Antecubital vein</td>
<td>Hct to 50%</td>
<td>Umbilical vein catheter FFP</td>
<td>Neonatal symptoms</td>
<td>BSID and neurological assessment at 1 and 2 years. Slosson IQ and WRAT test at 7 years</td>
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<tr>
<td>Bada</td>
<td>Not clearly stated</td>
<td>28</td>
<td>Only asymptomatic patients were randomized.</td>
<td>Radial artery Hct &gt; = 63%</td>
<td>Hct to 55%.</td>
<td>Route not stated Plasmanate</td>
<td>Cerebral artery Doppler measurements</td>
<td>BSID or Stanford Binet and neurological assessment at 30 months:</td>
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<tr>
<td>Ratriswadi</td>
<td>Not clearly stated</td>
<td>105</td>
<td>Only asymptomatic patients were randomized.</td>
<td>Central Venous HCT 65% or more</td>
<td>Hct to 60%</td>
<td>Route not stated</td>
<td>None</td>
<td>Gasel development at 1.5-2yrs</td>
</tr>
</tbody>
</table>

BNBAS = Brazelton Neonatal Behavioural Assessment Scale. BSID = Bayley Scales of Infant Development. WRAT = Wide range achievement test.
<table>
<thead>
<tr>
<th>Study</th>
<th>Inclusion/exclusion criteria</th>
<th>Randomisation</th>
<th>Masking of examiners</th>
<th>Completeness of follow up</th>
</tr>
</thead>
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<tr>
<td>Van der Elst</td>
<td>Clearly stated</td>
<td>Mode of randomization is not clearly stated</td>
<td>Examiner was masked to intervention status</td>
<td>Exact percentage follow up at 8 months not stated.</td>
</tr>
<tr>
<td>Goldberg</td>
<td>Clearly stated</td>
<td>Mode of randomization is not clearly stated</td>
<td>Examiners were masked to intervention status</td>
<td>There was complete follow up in the treated, 60% untreated.</td>
</tr>
<tr>
<td>Black</td>
<td>Clearly stated</td>
<td>Randomization by drawing a card from deck generated by a random number table.</td>
<td>Unclear</td>
<td>Two year follow up of 62%. Some data provided on failure of follow up. 7 year follow up of 49/93.</td>
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<tr>
<td>Bada</td>
<td>Clearly stated</td>
<td>Mode of randomization is not clearly stated</td>
<td>Examiners were masked to intervention status</td>
<td>Follow up was 67%.</td>
</tr>
<tr>
<td>Ratriswadi</td>
<td>Clearly stated</td>
<td>Alternate assignment</td>
<td>Unclear</td>
<td>Follow up was 38%</td>
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</table>
### Review:
Partial Exchange for Polycythemia in the Newborn

### Comparison:
01 Partial exchange for Polycythemia

### Outcome:
02 Presence of Developmental Delay at 24-30 months

<table>
<thead>
<tr>
<th>Study or sub-category</th>
<th>Exchange nN</th>
<th>Observation nN</th>
<th>RR (random) 95% CI</th>
<th>Weight %</th>
<th>RR (random) 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Block 1995</td>
<td>5/26</td>
<td>4/30</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dauda 1991</td>
<td>5/9</td>
<td>5/11</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>37</td>
<td>41</td>
<td></td>
<td></td>
<td>1.26 [0.62, 2.56]</td>
</tr>
</tbody>
</table>

Total events: 10 (Exchange), 9 (Observation)
Test for heterogeneity: Chi² = 0.02, df = 1 (P = 0.90), I² = 0%
Test for overall effect: Z = 0.84 (P = 0.52)

[Graph showing funnel plot with data points and summary statistics]
<table>
<thead>
<tr>
<th>Study or sub-category</th>
<th>Exchange nN</th>
<th>Observation nN</th>
<th>RR (random)</th>
<th>Weight %</th>
<th>RR (random) 95% CI</th>
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</thead>
<tbody>
<tr>
<td>Block1995</td>
<td>7/20</td>
<td>16/29</td>
<td>2.83</td>
<td>76.69</td>
<td>0.35 [0.22, 0.99]</td>
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<tr>
<td>Dadda 1991</td>
<td>1/9</td>
<td>0/11</td>
<td>23.31</td>
<td></td>
<td>3.60 [0.16, 79.01]</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>37</strong></td>
<td><strong>40</strong></td>
<td><strong>100.00</strong></td>
<td></td>
<td>0.73 [0.13, 4.18]</td>
</tr>
</tbody>
</table>

Total events: 8 (Exchange), 16 (Observation)
Test for heterogeneity: Chi² = 1.88, df = 1 (P = 0.19), I² = 40.5%
Test for overall effect: Z = 0.35 (P = 0.73)
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