Short and long term outcomes following partial exchange transfusion in the polycythaemic newborn: a systematic review

E M Dempsey, K Barrington

Background: Severe polycythaemia in the neonate may produce symptoms due to hyperviscosity and may be associated with serious complications. Partial exchange transfusion will reduce the packed cell volume.

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

Search strategy: Medline, EMBASE, and the Cochrane Controlled Trials Register of the Cochrane Library were searched. The following keywords were used: polycythaemia, partial exchange transfusion, hyperviscosity, and limited to the newborn. This covered years 1966–2004. Abstracts of the Pediatric Academic Societies and personal files were also searched.

Selection criteria: Randomised or quasi-randomised trials in term infants with polycythaemia 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: All data for each study were extracted, assessed, and coded separately. Any disagreements were resolved by discussion.

Main results: Six 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) after partial exchange transfusion in symptomatic or asymptomatic infants. There is no evidence of improvement in early neurobehavioural assessment scores (Brazelton neonatal behaviour 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. Necrotising enterocolitis is probably increased by partial exchange transfusion (relative risk 8.68, 95% confidence interval 1.06 to 71.1).

Conclusion: There is no evidence of long term benefit from partial exchange in polycythaemic infants, and the incidence of gastrointestinal injury is increased. The long term outcome is more likely to be related to the underlying cause of polycythaemia.

METHODS

Criteria for inclusion

Studies were included if they were randomised or quasi-randomised clinical trials, if the participants were newborn with documented central polycythaemia (defined as a central packed cell volume greater than or equal to 64%), and if the interventions consisted of a PET designed to reduce central packed cell volume to 60% or less, compared with observation only.

Outcome measures

(1) Long term neurodevelopmental, expressed as the proportion of infants with a neurological diagnosis, developmental delay, and/or motor abnormalities at 18 months or older. Alternatively, evaluation of cognitive or motor development using a validated continuous scale was acceptable.

(2) Short term neurological assessed by neurological and behavioural assessment scores.

Abbreviations: BNBAS, Brazelton neonatal behavioral assessment scale; NEC, necrotising enterocolitis; PET, partial exchange transfusion
### Table 1 Description of included studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Gestation</th>
<th>Sample size</th>
<th>Symptomatic/asymptomatic</th>
<th>Packed cell volume</th>
<th>Planned reduction</th>
<th>Mode of exchange</th>
<th>Short term follow up assessment</th>
<th>Long term follow up assessment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Van der Elst et al&lt;sup&gt;10&lt;/sup&gt;</td>
<td>Not clearly stated</td>
<td>49</td>
<td>No distinction made between symptomatic/asymptomatic. All symptoms considered minor</td>
<td>PCV of 65%</td>
<td>PCV to &lt;60%</td>
<td>Umbilical vein catheter. FFP</td>
<td>BNBAS and neurological assessment at 10 days</td>
<td>Neurological, developmental assessment at 8 months (similar to the Griffith development score)</td>
</tr>
<tr>
<td>Goldberg et al&lt;sup&gt;11&lt;/sup&gt;</td>
<td>Not clearly stated</td>
<td>20</td>
<td>No distinction made between symptomatic and asymptomatic</td>
<td>Venous PCV &gt;64% and hyperviscous. Antecubital vein</td>
<td>PCV to 50%</td>
<td>Umbilical vein catheter. FFP</td>
<td>BNBAS at 8 h, 24 h, 72 h, and 2 weeks</td>
<td>BSID and neurological assessment at 8 months</td>
</tr>
<tr>
<td>Black et al&lt;sup&gt;12&lt;/sup&gt;</td>
<td>“Term”</td>
<td>93</td>
<td>No distinction made between symptomatic and asymptomatic</td>
<td>Venous PCV 65% and hyperviscous. Antecubital vein</td>
<td>PCV 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>
</tr>
<tr>
<td>Bada et al&lt;sup&gt;13&lt;/sup&gt;</td>
<td>Not clearly stated</td>
<td>28</td>
<td>Only asymptomatic patients were randomised</td>
<td>Radial artery PCV &gt;63%</td>
<td>PCV to 55%</td>
<td>Route not stated. Plasmamine</td>
<td>Cerebral artery Doppler measurements</td>
<td>BSID or Stanford Binet and neurological assessment at 30 months</td>
</tr>
<tr>
<td>Ratrisawadi et al&lt;sup&gt;14&lt;/sup&gt;</td>
<td>Not clearly stated</td>
<td>105</td>
<td>Only asymptomatic patients were randomised</td>
<td>Central venous PCV 65% or more</td>
<td>PCV to 60%</td>
<td>Route not stated</td>
<td>None</td>
<td>Gassel development at 1.5–2 years</td>
</tr>
</tbody>
</table>

PCV, Packed cell volume; BNBAS, Brazelton neonatal behavioural assessment scale; BSID, Bayley scales of infant development; WRAT, wide range achievement test.
discuss the long term outcomes of symptomatic and asymptomatic patients. Bada et al.12 noted that gastrointestinal symptoms in 42% of patients after PET and in only 2% of the controls. They also noted in a separate publication that eight of the 43 infants who had PET (and none of the 50 controls) developed typical NEC with pneumatosis and clinical symptoms.5 No adverse events were reported in the studies of Goldberg et al.,13 14 both using a packed cell volume of 65% or more.

There are no randomised 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.17 However, there appears to be no clear evidence that the long term outcome of polycythaemic infants is worse in symptomatic patients, compared with those who were asymptomatic. Bada et al.13 evaluated the long term outcome of the 10 non-randomised symptomatic infants in their study, which do not appear to be substantially different from the outcomes of the asymptomatic infants in the randomised trial—for example, the scores on the Bayley scales of infant development were almost identical (90 ± 9 in the PET group and 88 ± 13 in the controls). Observational studies suggest that symptoms attributed to polycythaemia do improve after PET,19 20 but these are in any case transient, and the lack of controls prevents us from drawing any firm conclusions about the effect of PET on timing of resolution of symptoms.

### DISCUSSION

The current standard neonatal practice for performing a PET is (a) symptomatic with a packed cell volume of 65% or more17 or (b) asymptomatic with a packed cell volume of 70% or more. The Committee of the Fetus and Newborn of the American Academy of Pediatrics does not issue any definitive guidelines, stating that the accepted treatment of polycythaemia is PET.18 We identified five randomised trials of PET in polycythaemic newborns. The studies have small numbers of patients, use various definitions of polycythaemia based on packed cell volume, and have various follow up times. Only two studies evaluated the efficacy of PET in studies limited to asymptomatic patients,19 20 both using a packed cell volume of 65% or more.

<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>
<tbody>
<tr>
<td>Van der Elst et al10</td>
<td>Clearly stated</td>
<td>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 et al11</td>
<td>Clearly stated</td>
<td>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 et al12</td>
<td>Clearly stated</td>
<td>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. Follow up was 67%</td>
</tr>
<tr>
<td>Bada et al13</td>
<td>Clearly stated</td>
<td>Not clearly stated</td>
<td>Examiners were masked to intervention status</td>
<td>Follow up was 67%</td>
</tr>
<tr>
<td>Ratrisawadi et al14</td>
<td>Clearly stated</td>
<td>Alternate assignment</td>
<td>Unclear</td>
<td>Follow up was 38%</td>
</tr>
</tbody>
</table>

**Table 2 Methodological quality of included studies**

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

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Partial exchange transfusion

<table>
<thead>
<tr>
<th>Study or sub-category</th>
<th>Exchange (n/N)</th>
<th>Observation (n/N)</th>
<th>RR (random) (95% CI)</th>
<th>Weight (%)</th>
<th>RR (random) (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Black et al\textsuperscript{12}</td>
<td>7/28</td>
<td>16/29</td>
<td>76.69</td>
<td>23.31</td>
<td>76.69</td>
</tr>
<tr>
<td>Badda et al\textsuperscript{13}</td>
<td>1/9</td>
<td>0/11</td>
<td>0.45 (0.22 to 0.93)</td>
<td>3.60 (0.16 to 79.01)</td>
<td>0.45 (0.22 to 0.93)</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>37</td>
<td>40</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total events: 8 (exchange), 16 (observation)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for heterogeneity: $\chi^2 = 1.68, df = 1 \ (p = 0.19)$, $I^2 = 40.5%$</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Test for overall effect: $Z = 0.35 (p = 0.73)$</td>
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<td></td>
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<td></td>
</tr>
</tbody>
</table>

Figure 2. Forest plot of effect of partial exchange transfusion in polycythaemic newborn infants on the proportion of infants with a neurological diagnosis at 24–30 months of age. RR, Relative risk; CI, confidence interval.

What is already known on this topic

- Polycythaemia occurs in 2–5% of term neonates
- Partial exchange transfusion is generally advocated when the packed cell volume is greater than 70% in asymptomatic patients or greater than 65% in symptomatic patients

None of the studies that included both symptomatic and asymptomatic infants provided long term follow up information based on symptomatology. In particular, patients with severe neurological symptomatology (such as seizures) have not been reported separately, thus a possibility remains that such infants may 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 et al\textsuperscript{13} of asymptomatic infants assessed at 24 months or greater was unable to show any effect of PET on long term neurodevelopmental outcome. We combined the findings of this study with those of the much larger study of Black et al\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 the cause of the impaired long term outcome is the cause of the polycythaemia, usually intrauterine fetal hypoxia. Bada et al, for example, were unable to find an effect of PET, but noted from 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{\textdegree} Van der Elst et al\textsuperscript{11} reported that all infants followed to 8 months were neurologically normal and had “a developmental score appropriate for their age”. Goldberg et al\textsuperscript{10} examined 10 PET treated and six control infants and found 5/10 compared with 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 two studies that report NEC, 9/67 PET infants, compared with 0/75 controls developed this disorder. In both studies, PET was performed by umbilical catheterisation. These data suggest a temporal and causative relation 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 polycythaemia. There is, specifically, no evidence of a long term neurological benefit. Although the outcome of polycythaemic infants is poorer than that of concurrently enrolled infants without polycythaemia,\textsuperscript{10,13} this is probably related to the underlying cause of polycythaemia, 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 most of the 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 necrotising enterocolitis.

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Authors’ affiliations

E M Dempsey, K Barrington, Department of Pediatrics, McGill University Health Center, Montreal, Canada

Competing interests: none declared

REFERENCES

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