## *Brief Reports*

# Effect of Partial Exchange Transfusion in Asymptomatic Polycythemic LBW Babies

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*Manuscript received: August 6, 2002, Initial review completed: October 28, 2002; Revision accepted: August 19, 2003.*

*This randomized controlled trial was conducted to determine the effect of partial exchange transfusion in polycythemic babies. Forty five asymptomatic polycythemic babies with birth weight £ 2000 g were included and randomly assigned to undergo either partial exchange transfusion using isotonic saline within 4 hours of screening or routine medical management. Outcome measures were neonatal morbidity (especially hypoglycemia and neurological alterations) and mortality; developmental delays using DDST-II, neurological deficits, tone and DTR abnormalities over 18 months follow up period. The overall neonatal morbidity in this study was low and comparable in the two groups. Some of the polycythemic babies in the non-exchanged group found initially at 3 months age with "suspected development" grew out of their developmental delay at 18 months of age or later while those who underwent exchange transfusion and with retarded development at 3 months of age remained so even at 18 months of age.*

**Key words:** *Asymptomatic, Developmental delay, Exchange transfusion, Neonatal, Polycythemia.*

Neonatal polycythemia is a frequent diagnostic and management problem. The disorder is associated with transient, potentially reversible but sometimes life threatening insults to the heart, kidneys, lungs and intestines(1-5) in the neonatal period, whereas CNS involvement may leave permanent damage(5-9). Treatment of polycythemia in the neonatal period has included partial exchange transfusion. This study was undertaken to evaluate the efficacy of partial exchange transfusion in asymptomatic polycythemic LBW neonates in modifying neonatal morbidity and mortality, and preventing subsequent neurological sequelae and developmental delay.

## Subjects and Methods

This randomized controlled trial was conducted on asymptomatic polycythemic babies, during seventeen months period starting from March 1999. All intramural babies born in a tertiary level neonatal unit of a teaching hospital with birth weight £2000 g were screened at 6 to 8 hours of age for polycythemia. Polycythemia was defined as a peripheral venous hematocrit of 70% or greater at 6 to 8 hours of age(10). Polycythemic babies with following symptoms at or before screening were excluded from the study: central cyanosis, respiratory distress, congestive cardiac failure, hypoglycemia, and

convulsions or jitteriness.

*Outcome variables*

Neonatal morbidity (with special reference to hypoglycemia and neurological alterations) and mortality. Developmental delays in Gross motor, Language, Fine motor-adaptive and Personal-social sectors using DDST-II, neurological alterations in form of neurological deficits, tone and DTR abnormalities over 18 months follow up period.

*Randomization and Intervention*

Asymptomatic polycythemic babies were randomly assigned to undergo either partial exchange transfusion or routine medical management as per computer generated random number sequence placed in serial numbered opaque sealed envelopes. All exchange transfusions were done as early as possible within 4 hours of screening, preferably by peripheral route using isotonic saline. Total exchange volume was calculated by the formula [(PV Hct-Hct)/PV Hct] × (BV/Kg) × BW; where PV Hct = measured peripheral venous hematocrit level, Hct = desired hematocrit level (55%), BV/Kg = blood volume per kilogram of body weight, BW = birth weight in kilograms. The blood volume per kilogram of body weight in polycythemic neonates was obtained by nomogram designed by Rawlings *et al.*(11). As per unit policy, oral feeds at 60 ml/kg/day were started within 2 hours of birth. IV fluids were initiated at 60 ml/kg/day on day 1 of life for all birth weights and gestational ages, subsequent increments (usually 10 ml/kg/day) were based on weight pattern, urine output, *etc*.

*Data Collection*

Following enrolment, all polycythemic babies were observed in special care nursery unit for at least 48 hours for cyanosis, respiratory distress, CHF, hepatomegaly, jitteriness, convulsions, jaundice, NNEC, ICH, *etc.* Glucose level was checked in all babies to detect asymptomatic hypoglycemia by glucostix every 6-12 hours and if less than 40 mg%, a blood level measurement was obtained. Intravenous fluids were given for low blood glucose levels. Two babies received intravenous fluids for 6-8 hours following umbilical venous catheterization for the purpose of partial exchange transfusion. No baby received IV fluids for poor feeding. Neonatal morbidity and mortality were noted till 30 days of age in all babies followed up. Various maternal parameters relevant to development of polycythemia in newborn *e.g.*, age, parity, PIH and diabetes, *etc*. were also noted.

Laboratory investigations done in all polycythemic babies included hematocrit and blood sugar levels (glucostix and random blood sugar) at screening and 4 hours and 48 hours post exchange in exchanged/post enrolement in non-exchanged babies. All hematocrit values >65% were repeated and such babies whose average hematocrit level of the two readings was ³70% were included in the study. Cranial USG was done within one week of life.

*Follow up*

Babies were followed up at 3,6,9,12 and 18 months of postnatal age (age was adjusted for prematurity when indicated). Developmental assessment in four sectors, *i.e.*, Gross motor, Language, Fine motor-adaptive, and Personal-social using Denver Development Screening Test II (DDST-II)(12) was done at each visit by one of the authors (AK), as per details in the training manual. Standard neurological examination and medical history and physical examination including weight and head circumference were performed at each visit.

Data thus obtained were entered into computer using EPIINFO Version 6.0 software. Statistical analysis was done by using Student's t-test for means and Chi-square and Fischer exact test for proportions.

## Results

There were 732 newborns with birthweight £2000 g born during the study period. On screening, 53(7.24%) babies were polycythemic. Eight babies who were symptomatic at or before screening were excluded. The remaining 45 asymptomatic babies were randomized either to partial exchange transfusion (n = 22) or to routine medical management (n = 23) groups. One baby initially in non-exchanged group who developed symptomatic hypoglycemia at 32 hours of age was exchanged but has been retained for analysis purpose in the group to which he was originally randomized (intention-to-treat).

Baseline neonatal parameters like sex, birth weight, gestational age, and ponderal index were comparable in both groups (*Table I*). Apgar scores were comparable in the two groups. Mothers of 6 and 5 polycythemic babies in exchanged and non-exchanged groups respectively had PIH in the perinatal period while none of the mothers were diabetic in both the groups. Maternal age and parity were comparable in two groups. Hematocrit values at enrolment were comparable between groups (p = 0.19). Following exchange transfusion, the exchanged group had significantly lower hematocrit values compared to non-

**TABLE I**–*Parameters of Neonates in Two Groups*

| | Group I<br>Asymptomatic Exchange<br>(n = 22) | Group II<br>Asymptomatic Non-exchange<br>(n = 23) |
|---|---|---|
| **Age at screening** (hours)<br>Mean (± SD) | 7.7 (4.6) | 8.3 (5.7) |
| **Sex (%)** | | |
| Male | 12 (54.5) | 10 (43.5) |
| Female | 10 (45.5) | 13 (56.5) |
| **Birth weight** (g) | 1720 (1000-2000) | 1760 (1250-2000) |
| Median (range) | | |
| **Gestational age** (weeks) | 36.7 (3.3) | 37.2 (2.4) |
| Mean (± SD) | | |
| **Growth status (%)** | | |
| SGA | 19 (86.4) | 19 (82.6) |
| AGA | 3 (13.6) | 3 (13.0) |
| LGA | 0 | 1 (4.4) |
| **Ponderal index** | 2.26 (0.26) | 2.15 (0.23) |
| Mean (± SD) | | |
| **Mean hematocrit (SD)** | | |
| Enrolment | 76.9 (4.5) | 75.3 (3.4) |
| After 4 hours | 55.3 (4.9) | 70.8 (6.2) |
| After 48 hours | 53.7 (7.1) | 66.9 (7.3) |

exchanged group after 4 hours, and 48 hours period (P <0.001). The mean isotonic saline volume required for exchange was 29 ml/kg body weight in the exchanged group.

Approximately half of the babies in both the groups did not develop any symptoms (*Table II*) and remained euglycemic during entire period of observation. The frequency of hypoglycemia, apnea and jaundice were comparable in both groups. Majority of hypoglycemic babies were small for gestational age (six each in both groups). Cerebral edema was detected on cranial USG in 2 hypoglycemic babies in non-exchanged group. Neurolgoical examination performed on all the 19 (group I) and 16 (group II) babies on day 7 of life and 13 babies (in each group) on day 30 of life was normal. Out of 5 neonatal deaths in the exchanged group, evidence of systemic infection could be detected in 2 babies within 7 days of exchange transfusion (one 29 weeks gestation - 1000 g birth weight-hematocrit 74% with culture positive sepsis on day 6 of life, other 35 weeks gestation - 1400g birth weight-hematocrit 73% with culture positive sepsis and ventriculitis on day 7 of life). Another baby with hematocrit of 80% died of asphyxiating thoracic dystrophy on day 4 of life. In late neonatal deaths, one 37 weeks gestation - 1650 g birth weight-hematocrit 73% baby died of pneumonia with pneumothorax on day 17 of life while cause of death could not be ascertained in a 35 weeks-1300 g birth weight-hematocrit 75% died on day 30 of life. In non-exchanged group, one baby of 32 weeks gestation - 1250 g birth weight-hematocrit 72.7% died of culture positive sepsis on day 4 of life.

*Follow-up Data*

Developmental assessment done at 3 months age using DDST-II revealed more babies in "suspect development" among non-exchanged group than in exchanged group (57.1% vs 27.3%, p = 0.22). This trend gradually narrowed at subsequent follow up visits at 6, 9, 12 and 18 months age (*Table III*). On further analysis of gross motor sector, similar trend persisted in non-exchanged and exchanged groups of babies. In fine motor-adaptive and personal-social sectors, the initial

**TABLE II–***Comparison of Neonatal Outcome in Two Groups*

| | Group I (N = 22) | Group II (N = 23) | P value (corrected) |
|---|---|---|---|
| Asymptomatic & Euglycemic (%) | 11 (50.0) | 11 (47.8) | 0.76 |
| **Symptoms** | | | |
| Apnea | 2 | 2 | |
| Jaundice | 2 | 1 | |
| **Investigations** | | | |
| Hypoglycemia | | | |
| Frequency (%) | 7 (31.8) | 9 (39.1) | 0.61 (0.84) |
| Age of onset (hours ) (± SD) | 8.9 (4.3) | 11.5 (7.6) | 0.60 |
| Duration of IV Dextrose required (Hours) (± SD) @ < 8 mg/kg/min | 28 (19.8) | 43.1 (32.5) | 0.45 |
| USG Cranium (abnormal/total) | 0/18 | 2/18 | |
| **Death** | 5 | 1 | |

**TABLE III–***Comparison of Developmental Outcome in Two Groups Evaluated by DDST-II*

| Age in months | Exchanged group | | % | Non-exchanged group | | % | P value |
|---|---|---|---|---|---|---|---|
| | Total No. of children examined | Children with suspected development | | Total no of children examined | Children with suspected development | | |
| 3 | 11 | 3 | 27.3 | 7 | 4 | 57.1 | 0.22 |
| 6 | 10 | 3 | 30.0 | 7 | 3 | 42.9 | 0.48 |
| 9 | 10 | 3 | 30.0 | 7 | 3 | 42.9 | 0.48 |
| 12 | 8 | 3 | 37.5 | 5 | 2 | 40.0 | 0.69 |
| 18 | 8 | 3 | 37.5 | 5 | 1 | 20.0 | 0.49 |

abnormalities seen disappeared completely in both the groups at 18 months follow up. Only one baby each had delayed language development at 18 months follow up out of 5 and 8 babies examined in non-exchanged and exchanged groups respectively.

On follow up neurological examination, no focal deficits were seen in either group throughout the eighteen months period of observation. While only one baby had hypertonia at 3 months of age in exchanged group, additional 2 babies developed hypertonia out of 8 babies followed up at 18 months of age. In non-exchanged group over 18 months follow up, only 1 baby was noted to have transient hypertonia at 12 months age. In the exchanged group, brisk DTR were noticed in 4 babies (36.4%) at 3 months age which persisted till 18 months follow up. In non-exchanged group, 28.6% babies were noted to have increased DTR which completely disappeared at 18 months.

## Discussion

Neonatal polycythemia-hypervisocity syndrome has been known for more than three decades to be associated with significant morbidity and mortality in the neonatal period(7). Asymptomatic polycythemia has also been associated with an increased risk of later neurologic and developmental impairment(8,9). In most nurseries, viscosity determinations are not readily available as a routine clinical tool; therefore hematocrit values are relied on for diagnosis of this syndrome(6). Since hematocrit level is influenced by timing of sample, a venous hematocrit value of $\geq$68% at 6 hours of age is an accepted norm for defining neonatal polycythemia(10). We defined venous hematocrit of $\geq$70.0% at 6-8 hours of age as polycythemia for simplicity of calculation and quest for better, less invasive criteria of diagnosis(6).

As reported by other investigators also(4,6,9), approximately half of the polycythemic babies in the present study in both exchanged and non-exchanged groups remained asymptomatic and euglycemic throughout the neonatal period of observation. The presence of asymptomatic hypoglycemia in seven out of 22 exchanged (31.8%) and nine out of 23 non-exchanged babies (39.1%) is in conformity with the incidence as reported by other workers(9,13) but according to Black *et al.*(14), the incidence was 16% and 12% in

## Key Messages

- Neonatal morbidity in asymptomatic polycythemic (peripheral venous hematocrit ³70% at 6-8 hours of age) LBW babies is low, with no neurological deficits at 30 days of age and is not influenced by partial exchange transfusion.
- Some of the polycythemic babies in the non-exchanged group found initially at 3 months age with "suspected development" grow out of their developmental delay at 18 months of age or later while those who underwent exchange transfusion and with retarded development at 3 months of age remain so at 18 months of age.

exchanged and non-exchanged babies. Other morbidities (apnea and jaundice) had minor contribution in both the groups. No neurological alterations were present in any of the babies examined at the age of 7 days and 30 days of follow up. Thus overall neonatal morbidity in this study (50%) is lower than reported in literature(13). It is because we excluded all the eight babies who were symptomatic before randomization and had to be exchanged. Moreover, since we did not routinely investigate all asymptomatic babies, we might have missed some of the subclinical organ involvement as upto 20% of polycythemic babies may have laboratory abnormalities without overt symptoms(13).

The early neonatal deaths of 2 babies in the exchanged group due to culture positive sepsis can not be conclusively ascribed due to the process of exchange transfusion as both babies underwent peripheral exchange transfusion only and were very low birth weight preterm babies otherwise also susceptible to infection. Late neonatal mortality is unlikely due to partial exchange transfusion or polycythemia itself directly.

The developmental delay in hyperviscous children varies with age(8). The serial development assessment at 3 months interval during infancy and 6 monthly thereafter in exchanged babies revealed almost a constant number *i.e*., one third children to be in "Suspected" development throughout the period of observation. On the other hand in non-exchanged group, three babies improved their developmental delay over 18 months period. Gross motor sector also revealed similar trend over this period. This trend of development in two groups indicates that some of the polycythemic babies in the non-exchanged group found initially at 3 months age with "suspected development" grew out of their developmental delay at 18 months of age or later while those who underwent exchange transfusion and with retarded development at 3 months of age remained so at 18 months of age. Other sectors of development in Fine motor-adaptive, Language and Personal-social areas, did not have many babies with developmental delay at 18 months follow up. The significance of hypertonia and exaggerated DTR in the absence of any focal neurological deficits at 18 months age in the exchanged group babies is difficult to ascertain and requires further followup.

Thus, if we treat symptomatic polycythemic babies before 6-8 hours of age with partial exchange transfusion, neonatal morbidity in the remaining asymptomatic polycythemic babies is low and is comparable in exchanged and non-exchanged groups, including no neurological deficits at 30 days of age. The growing out of some of the babies out of their developmental delay with time in the non-exchanged group requires further

confirmation as present study has inadequate sample size with some of the babies lost to follow up at subsequent visits.

## Acknowledgement

The authors gratefully acknowledge the contribution of Dr. Dheeraj Shah in helping initial enrolment of patients for the study.

*Contributors:* Both AK and SR conceived and designed the study. AK conducted and supervised the study, including DDST-II, data collection, analysis, drafting the manuscript and will act as the guarantor for the paper. SR did the critical evaluation of the manuscript.

*Funding:* None.

*Competing interests:* None stated.

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