RESEARCH PAPER

Fluid Supplementation *versus* No Fluid Supplementation in Late Preterm and Term Neonates with Asymptomatic Polycythemia: *A Randomized Controlled Trial*

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Objective: To compare supplemental intravenous fluids with no supplementation in asymptomatic polycythemic late preterm and term neonates.

Methods: 55 infants with venous haematocrit of 65-75 were randomly allocated to receive either 25 mL/kg IV normal saline over 6-8 hours or routine fluids. They were followed up for 48 hours.

Results: There was no significant difference between fluid supplementation and control groups regarding need for partial exchange transfusion [6/27 (22.2%) *vs* 8/28 (28.6%); *P*=0.59].

Conclusions: We did not find any evidence of clinical benefit with IV fluid supplementation in late preterm and term neonates with asymptomatic polycythemia (PCV 65-75).

Keywords: *Exchange transfusion, Fluid therapy, Hematocrit, Management*.

Polycythemia is a common problem faced in day-to-day neonatal practice [1,2]. It is known to be associated with short term symptoms as well as long term neurological adverse effects [3,4]. Treatment of polycythemia remains controversial. Partial exchange transfusion (PET) is often performed in symptomatic neonates with hematocrit >65% and asymptomatic neonates with hematocrit >75% [5-7]. PET though associated with earlier improvement of symptoms, has not shown long-term benefits [8]. Management of neonates with asymptomatic polycythemia (PCV 65-75%) is not clear. PET is not recommended in them due to lack of demonstrated benefit and fear of complications [6]. Fluid supplementation is often used as a mode of therapy in such neonates, but this practice is not backed by evidence [6]. We planned a study to compare supplemental parenteral fluids with no supplemental fluids for decreasing the need for PET among asymptomatic polycythemic neonates (PCV 65-75).

METHODS

We conducted the study over one-year in a level III newborn unit in a tertiary-care institute in India. Institute ethics committee approved the protocol. Of high-risk neonates screened for polycythemia, infants ≥34 weeks of gestation with a venous hematocrit ranging from 65-75% measured at ≥6 hours of age were considered eligible [3,9,10]. Our unit policy is to screen babies with risk factors for polycythemia routinely at 6,12 and 24 hours of age and whenever clinically indicated after this period. Babies got recruited whenever they were diagnosed with polycythemia starting from 6 hours of life. We spun venous blood collected in two capillary tubes for 3 minutes at 12000 rpm using SIGMA 1-15 micro-hematocrit centrifuge and measured hematocrit with micro hematocrit reader [11]. We recorded the value only when both tubes agreed within 1% of each other. We excluded neonates with clinical symptoms, signs or laboratory abnormalities known to be commonly associated with polycythemia (blood glucose <40 mg/dL, serum bilirubin in phototherapy range) and those with features of dehydration (presence of two or more of the following, >4% weight-loss over 24 hours, depressed anterior fontanel, dry oral mucosa, capillary refilling time >2 seconds, tachycardia, poor peripheral pulses).

The key outcome was need for PET within 48 hours of randomization. Indications for PET were either (*i*) Hematocrit >75% anytime from 4 hours after randomization until end of study period, and/or (*ii*) development of any clinical or laboratory abnormality known to be associated with polycythemia with hematocrit ≥65% during study period. Secondary outcomes included

hematocrit values at 4, 8, 16, 24, 32, 40 and 48 hours after randomization and failure of hematocrit to fall below 65% at end of 8 hours.

We enrolled neonates after obtaining informed written consent from one of the parents. We randomly allocated subjects by stratified block randomization. Subjects were stratified by initial hematocrit into Stratum A (hematocrit 65–70) and Stratum B (hematocrit 71–75). Even-numbered, permuted blocks of randomly varying sizes were generated, with a 1:1 allocation ratio. Random sequence was generated online from a website. Serially numbered sealed opaque envelopes were used to conceal allocation. Randomization and intervention were done within 15 minutes of enrollment.

Group 1 received supplemental intravenous fluids (25 mL/kg normal saline over 6–8 hours) in addition to maintenance fluids and Group 2 received only maintenance fluids as per unit protocol. The treating physician decided the amount and mode of maintenance fluid administration (whether direct breastfeeds, spoon feeds, tube feeds or intravenous fluids). Both groups were followed up for next 48 hours. The trial was open-label.

Due to lack of data on the proportion of subjects with asymptomatic polycythemia who require PET without fluid supplementation, we recruited an arbitrary sample size of 50 subjects for the sake of convenience. We compared categorical outcome variables by Chi square test or Fisher's exact test; normally distributed variables by Student's t test, variables with skewed distribution by Mann Whitney U test; and equality of means for repeated measurements by repeated measures ANOVA. *P* value of less than 0.05 was considered significant. We used statistical software package SPSS version 13.0 for analysis.

TABLE I COMPARISON OF BASELINE CHARACTERISTICS BETWEEN FLUID SUPPLEMENTATION AND NO SUPPLEMENTATION GROUPS

Variable	*Fluid supplementation Group 1(n =27)*	*No fluid supplementation Group 2 (n = 28)*
Males	17 (63)	11 (39.3)
Gestational age* (weeks)	36 (34,37)	36 (34.3,37)
Birthweight * (g)	1896 (1378,2100)	1749 (1519, 2246)
Caesarean delivery	13 (48.1)	13 (46.4)
PIH in mother	15 (55.6)	13 (46.4)
Twin delivery	5 (18.5)	2 (7.1)
Intrauterine growth status		
AGA	9 (33.3)	5 (17.9)
SGA	17 (62.9)	21 (75)
LGA	1 (3.7)	2 (7.2)
Need for resuscitation	2 (7.4)	3 (10.7)
Cord arterial pH#	7.21 (0.1)	7.20 (0.8)
At Enrolment		
Age *(hours)	12 (7, 24)	6 (6, 14.5)
Mean PCV (%)#	69.1 (2.5)	68.9 (2.7)
PCV strata		
PCV 65-70	21 (77.8)	21 (75)
PCV 71-75	6 (22.2)	7 (25)
Weight *(g)	1810 (1352, 2070)	1715 (1497, 2195)
HR#	135 (7)	133 (8)
RR#	47 (5)	45 (6)
Liver span *(cm)	4.5 (4, 5)	4 (4, 4.9)
Mode of maintenance fluid		
Oral	21 (77.8)	21 (75)
Parenteral	1 (3.7)	4 (14.3)
Oral and parenteral	5 (18.5)	3 (10.7)

*Values in Number (%), *median (IQR) or #mean (SD).*

RESULTS

Of the 121 eligible neonates, 55 were enrolled after excluding 66. We randomly allocated 27 subjects to Intravenous fluid supplementation group and 28 to No fluid supplementation group. Both groups were comparable regarding presence of underlying risk factors for polycythemia (***Table* I**). All baseline characteristics were balanced between the two groups, except median age at enrollment (6 hours *vs* 12 hours). The least difference expected in age at enrollment was 6 hours as screening was done only at 6 hour intervals and this difference was due to random chance.

The primary outcome – need for PET – was not significantly different between the two groups. Six of 27 neonates in group 1 (22.2%) required PET compared to 8 of 28 (28.6%) in group 2. The relative risk was 0.78 (95% CI: 0.26, 2.19). Relative risk was not significantly different in subgroups analyzed as per PCV strata (Stratum A 0.87: 95% CI 0.3,2.49 Stratum B 0.64: 95% CI 0.07, 5.73) The proportion of neonates who remained polycythemic at the end of fluid supplementation [17 (63%) *vs* 21 (75%) *P*=0.33] and changes in PCV within subjects over a period of 48 hours also did not differ significantly between the two groups. Clinical parameters measured 4th hourly over 12 hours for possibility of circulatory overload did not differ significantly between the two groups (***Table* II**).

TABLE II COMPARISON OF OUTCOMES BETWEEN FLUID SUPPLEMENTATION AND NO SUPPLEMENTATION GROUPS

Outcome	*Fluid supplementation (n=27)*	*No fluid supplementation(n=28)*	*P value*
Need for PET	6 (22.2)	8 (28.6)	0.59
Polycythemic at 8 hours	17 (63)	21 (75)	0.33
*Change in PCV over time**			0.19
Baseline	68.9 (0.6)	69.2 (0.5)	
4 hrs.	67.2 (0.8)	66.6 (0.8)	
8 hrs.	66.1 (0.8)	64.5 (0.8)	
16 hrs.	64.9 (0.9)	64.5 (0.9)	
24 hrs.	64.1 (0.9)	63.6 (0.9)	
32 hrs.	63 (1.2)	61.2 (1.2)	
40 hrs.	62.4 (1.2)	59.7 (1.2)	
48 hrs.	62.4 (1.4)	58.8 (1.4)	
*Change in weight over time (g)**			0.92
Baseline	1859 (558)	1953 (743)	
8 hrs.	1875 (554)	1843 (560)	
*Change in HR over time**			0.43
Baseline	135 (7)	133 (8)	
4 hrs.	137 (6)	136 (6)	
8 hrs.	137 (7)	135 (9)	
12 hrs.	135 (5)	135 (7)	
*Change in RR over time**			0.25
Baseline	47 (5)	45 (6)	
4 hrs.	46 (5)	44 (6)	
8 hrs.	46 (5)	45 (6)	
12 hrs.	46 (5)	44 (5)	
*Change in liver span over time**			0.05
Baseline	4.4 (0.5)	4.3 (0.5)	
4 hrs.	4.5 (0.5)	4.4 (0.6)	
8 hrs.	4.4 (0.6)	4.4 (0.6)	
12 hrs.	4.4 (0.6)	4.4 (0.6)	

*Values in Number (%) or *mean (SD).*

DISCUSSION

Although intravenous fluid supplementation is often used to manage neonates with asymptomatic polycythemia, there has been no controlled trial conducted so far to evaluate its efficacy. Morag, *et al.* [6] advocated restrictive management with fluid supplementation in asymptomatic polycythemia (PCV 70-75) in a retrospective study without controls. We chose a gestational age cut off of ≥34 weeks as polycythemia is more common in them and as we were unsure about the safety of this intervention in very premature neonates [2,12]. We were unable to detect significant hemodilution with 25 mL/kg of supplemental isotonic fluid administered to polycythemic neonates, as there were no significant inter-group differences in PCV over a period of 48 hours. We suggest the possibility that a significant fraction of the supplemental intravenous fluids administered got redistributed to the extravascular fluid compartment. Falk, *et al.* [13] had shown earlier that crystalloids move freely across fluid compartments and only less than 25% of saline(crystalloid) is retained in the intravascular space at one hour following intravenous transfusion unlike colloids.

We hypothesize that the background fall in hematocrit noted in both the groups and attributed to the natural course of polycythemia may also account for the lack of effect. This spontaneous fall has been described in earlier studies [14,15]. Body water estimates in

WHAT THIS STUDY ADDS?

- Intravenous fluid supplementation of 25 mL/kg of normal saline administered to neonates with asymptomatic polycythemia (PCV 65-75) did not reduce the need for partial exchange transfusion.

polycythemic neonates report normal to increased circulating fluid volume [16,17]. It is possible that only dehydrated polycythemic infants benefit from fluid supplementation. We had excluded dehydrated subjects and absence of dehydration in our subjects could be another reason for the lack of effect of the intervention.

We consider our small sample size as a major limitation. Our study was underpowered to detect difference of 6.5% demonstrated in need for PET between the two arms. The confidence interval was wide and does not exclude clinically relevant outcomes. We evaluated only the short-term outcomes and not long-term implications of such intervention.

To conclude, we were unable to detect clinical benefit of intravenous fluid supplementation with 25 ml/kg normal saline in neonates with asymptomatic polycythemia (PCV 65-75). We believe our study will initiate fresh thinking and research into the distribution of body fluid among the various compartments and the factors influencing fluid shifts across these compartments in polycythemic infants.

Contributors: MS: conceived the study and its design, data acquisition, data analysis, interpretation and drafting the work; SD: designed the study, data analysis and interpretation, and critically revised the draft and intellectual content. AN: contributed critically to the design, data analysis, data interpretation and intellectual content. All authors are accountable for the accuracy of data and accountability of the original work done.

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