Original Research Article

A randomised control trial comparing the efficacy of cord milking over the delayed cord clamping on serum ferritin level in preterm neonates at 6 weeks of age

Sahana Devadas, Roshni R.*, Malleesh K.

Department of Paediatrics, Bangalore Medical College and Research Institute, Bangalore, Karnataka, India

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*Correspondence:

Dr. Roshni R.,

E-mail: roshu.mmc@gmail.com

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ABSTRACT

Background: Perinatal iron deficiency has received little attention in the past. Umbilical cord milking is a type of placental transfusion, they serve to potentially enhance neonatal blood volume and consequently the iron stores after birth. Among the neonates, the preterm infants are sick and vulnerable babies who are already deprived of iron stores. The aim of this study was to evaluate the effect of cord milking on ferritin values amongst preterm neonates.

Methods: This is a hospital based randomized control trial which included the babies born at 29-36 weeks of gestation. The babies were randomized to two intervention groups; cord milking and delayed cord clamping group. Detailed clinical history taken, including details of labour and clinical examination. Blood samples were analysed for ferritin as required at 6 weeks of post-natal age.

Results: Neonates under cord milking group had higher ferritin values (249.04 ± 21.93 ng/mL) as compared to those neonates under delayed cord clamping group (179.66 ± 32.94 ng/mL) and this was statistically very significant ($p < 0.001$).

Conclusions: In preterm neonates, umbilical cord milking results in improved iron status as shown by higher ferritin values at 6 weeks of life. UCM can be used as placental transfusion strategy in preterm neonates for improving iron status and preventing anemia of prematurity.

Keywords: Anemia of prematurity, Ferritin, Placental transfusion, Umbilical cord milking

INTRODUCTION

Perinatal iron deficiency has received little attention in the past, due to assumption that infants are protected from iron deficiency unless the mother is markedly anemic. In a survey in India, 70% of infants between 6 and 11 months of age were found to be anaemic.¹ To enhance iron transfer from placenta and umbilical cord to baby, interventions like umbilical cord milking and delayed cord clamping have received a lot of scientific attention.^{2,3} They serve to potentially enhance neonatal blood volume and consequently iron stores after birth.

The blood flow in the umbilical arteries and veins usually continues for a few minutes after birth. The additional blood volume transferred to the baby during this time is known as placental transfusion.

Delayed cord clamping (DCC) in which clamping of cord is delayed by 30 to 180 s has been shown to improve the haematological status in both preterm and term infants.⁴ Umbilical cord milking (UCM) is a method of rapid transfer of cord blood to baby by means of squeezing or stripping of cord toward the baby from the maternal end.¹

Preterm infants are sick and vulnerable babies who are already deprived of iron stores, are more vulnerable for complications like IVH (Intraventricular haemorrhage), Necrotizing enterocolitis (NEC), Anaemia of prematurity thus are at the greatest need for the advantages of placental transfusion. The total body iron (TBI) content at birth in healthy full-term infants is 75ml/kg with iron concentration in hemoglobin of approximately 3.4 mg/g, thereby a 3 kg infant, would receive 46-60 mg of iron as hemoglobin from this placental transfusion.^{5,6} If authors estimate that a new-born infant requires approximately 0.7 mg of iron per day for growth and development, maintenance of hemoglobin levels and myoglobin and enzyme levels in muscle and other tissues, 46-60 mg would be equivalent to roughly 1-3 months of infant iron requirements. Likewise, immediately clamping the umbilical cord will deprive the infant of a substantial portion of TBI at birth. In preterm neonates, this measure of extra iron would make significant differences to growth during infancy. Thus, the purpose of this study was to testify that umbilical cord milking is an efficient placental transfusion strategy over delayed cord clamping to improve iron status among the preterm neonates as shown by higher ferritin levels at 6 weeks of life.

METHODS

A Randomized control trial conducted in Preterm neonates (29-36 completed weeks) born in hospitals attached to Bangalore Medical College and Research Institute, Bengaluru, India. Study was conducted for the period of November 2017 to May 2019.

Inclusion criteria

Preterm neonates (29-36 completed weeks) (assessed by Ballard's chart) delivered either vaginally or by lower segment caesarean section at the institute and willing to participate in the study.

Exclusion criteria

- Umbilical cord length of <25cm
- Non vigorous at birth (requiring positive pressure ventilation)
- Multiple births
- Rh factor negative pregnancy
- Retroviral positive mother
- Hydrops fetalis
- Cord prolapsed
- Cord anomalies like true knot
- Babies born to mothers with placental complications such as placental abruption, placental implantation disorder.

Outcome

Primary outcome

- Ferritin values at 6 weeks of age

Secondary outcomes

- Admission temperature
- Mean arterial pressure (MAP) at 6 hours
- MAP at 24 hours
- Maximum serum bilirubin values
- Need for phototherapy
- Grade I - IV IVH

Sample size

Based on previous study, Kumar et al.⁷ The mean and standard deviation of ferritin levels at 6 weeks in early cord clamping (ECC) group is 237.5±118.6 ng/mL and UCM group is 428.9±217.60 ng/mL and assuming power is 80% and alpha error is 5% with two sided, the minimum require sample size is 13 in each group.

$$n = \frac{(Z_{\alpha} + Z_{\beta})^2 * 2 * \delta^2}{(\mu_1 - \mu_2)^2}$$

μ_1 = Mean Ferritin Levels in ECC group

μ_2 = Mean Ferritin Levels in UCM group

δ^2 = Combined Standard deviation

Z_{α} = Significance Level

Z_{β} = Power

Calculation

$$n = \frac{(1.96 + 0.84)^2 * 2 * 175.24^2}{(428.9 - 237.5)^2}$$

$$= \frac{7.84 * 481518}{36633.96}$$

$$n = 13$$

$$n_1 = n_2 = 26 \text{ in each group}$$

Considering 30% attrition rate. Sample size calculated was 39. A sample size of 85 in each group was taken for better validation of results.

Group 1: Neonates in whom umbilical cord milking done.

Group 2: Neonates in whom delayed cord clamping done.

Study procedure

After obtaining institutional ethics committee clearance and written informed consent neonates born with gestational age less than 37 weeks as per New Ballard's Score fulfilling the inclusion and exclusion criteria were enrolled in the study.

The subjects were randomly allocated into two groups using computer generated random numbers where even numbers were assigned to the intervention group: umbilical cord milking group and odd numbers were

assigned to the control group: delayed cord clamping group.

Immediately after delivery, the preterm neonate was assessed for any exclusion criteria. If fulfilling the inclusion criteria, then the umbilical cord was cut at a distance of one artery forceps from the mothers introitus. The length of the Kocher straight artery forceps is 25 cm. This was uniformly used for clamping the cord.

In the intervention group, umbilical cord of the neonates was raised and milked from the cut end towards the baby 3 times and clamped at 2-3 cm. The time to milk the umbilical cord was ensured by the wall mounted clock available in the delivery room. Whereas in the control group, umbilical cord was clamped after delay of 30 sec.

Data collection

All neonates received care in the NICU as per unit protocol. Non-invasive mean arterial pressures were checked at 6 hours and 24 hours of life. Babies were monitored for jaundice and IVH (detected by neuro sonogram (NSG) on day 3 or earlier if clinically indicated). For neonates with <35 weeks Based on Maisel's operational or therapeutic threshold for hyperbilirubinemia in preterm and for 35-36 weeks gestational age AAP (American academy of pediatrics) chart was followed.^{8,9}

All the neonates were followed up at the multidisciplinary follow up clinic the Neonatal Follow Up clinic (NFC). In the NFC, the babies were assessed for growth and development. (according to Trivandrum Development Screening Chart). Blood samples were drawn in plain tubes to assess ferritin at 6 weeks of postnatal age. Serum ferritin was measured by chemiluminescence method using Cobas 6000. The data collected was entered into a predesigned proforma.

Statistical analysis

The Statistical analysis was performed by STATA 11.2 (College Station TX USA). Shapiro Wilk test were used to check normality. Students t-test were used to find significance difference between the birth weight, gestational age, MAP, peak bilirubin values and ferritin levels at 6 weeks with groups (UCM and DCC) respectively and its expressed as mean and standard deviation, $p < 0.05$ considered as statistically significant.

RESULTS

Out of total 32458 total births during study period (November 2017-May 2019), there were 9542 preterm births. Among these preterm births, 372 were assessed for eligibility.

Among these 171 babies (36 multiple births, 14 Rh negative pregnancy, 82 required resuscitation, 15 refused

consent, 24 had placental abnormalities) were excluded and 201 babies were randomized. All randomized babies received allocated intervention. Figure 1 shows the trial flow of the study.

Figure 1: Trial flow of study.

The mean gestational age of the neonates enrolled in both the intervention groups were similar; 33.09 ± 1.51 weeks in UCM group and 33.23 ± 1.59 weeks in DCC group. The distribution of the gestational age in each intervention group was similar with majority of neonates belonging to 34-36 weeks followed by 32-33 weeks gestation (Table 1). The mean birth weight of neonates enrolled in the UCM group was 1.54 ± 0.18 kilogram and that in DCC group was 1.58 ± 0.16 kilogram. Most of the neonates were 1500-1799 g followed by 1200-1499 g. There were few neonates with birth weight 1800-1999 grams (Table 1). 62 % of neonates in the UCM group were male and 48 % neonates in DCC group were male (Table 1). 88 % of neonates in the UCM group and 95 % neonates in DCC group were born through vaginal delivery. Out of total 170 neonates, 157 neonates received antenatal steroids, 87% in UCM group received antenatal steroids and 97% in DCC group received antenatal steroids. Amongst the 170 neonates enrolled, 50 mothers had PPROM (Preterm premature rupture of membranes); 29 in UCM group and 21 in DCC group. 7 mothers had short spacing; 1 in UCM group and 6 in DCC group. Mothers of the 4 neonates those were enrolled in the UCM group had UTI.

It was observed that the neonates under UCM group (249.04 ± 21.93 ng/mL) had higher ferritin values as compared to those neonates under DCC group (179.66 ± 32.94 ng/mL) and this was statistically very significant with p value < 0.001 . There was no significant difference observed in the admission temperature amongst both the groups (Table 2).

Table 1: Comparison of characteristics among both the groups.

Characteristic	Cord milking group (n=85)	Delayed cord clamping (n=85)
Gestational age (weeks)*	33.09±1.51	33.23±1.59
Gestational age [#]		
28-31 weeks	10(11.7%)	13(15.3%)
32-33 weeks	37(43.5%)	25(29.4%)
34-36 weeks	38(44.7%)	47(55.2%)
Birth weight (g)*	1.54 ± 0.18	1.58± 0.16
Birth weight		
1200-1499 g	32(37.6%)	15(17.6%)
1500-1799 g	46(54.1%)	65(76.4%)
1800-1999g	7(8.2%)	5(5.9%)
Gender		
Male	53 (62%)	41 (48%)
Female	32 (38%)	44 (52%)
Type of delivery		
LSCS	10 (12%)	4 (5%)
Vaginal	75 (88%)	81 (95%)
Antenatal steroids		
Dexamethasone	74 (87%)	83 (97%)
No Antenatal steroids	11 (13%)	2 (3%)
Obstetric risk factors		
Nil	50(59%)	58 (68%)
PPROM	29 (34%)	21 (25%)
Previous LSCS	1 (1%)	
Short Spacing	1 (1%)	6 (7%)
UTI	4 (5%)	

*mean and standard deviation (SD)

number (percentages shown in parentheses)

Babies enrolled in UCM had lower mean arterial pressures (40.89±2.50 mm Hg and 39.21±1.42 mm Hg at 6hours and 24 hours of life respectively) as compared to those neonates in DCC (41.87±1.78 mm Hg and 39.65±1.27 mm Hg at 6hours and 24 hours respectively). (Table 2) This was significant.

The maximum serum bilirubin values were nearly the same (11.99±1.36 mg/dL and 12.12±1.29 mg/dL in UCM group and DCC group respectively) that did not show any substantial difference. Likewise, there was no substantial difference in need for phototherapy in both the groups as well (Table 2).

Among 170 neonates enrolled in the study, IVH was observed in 29 neonates, with no significant difference in incidence of IVH among the groups. All the IVH that were observed were of grade 1 (Table 2).

There was no mortality observed amongst the neonates enrolled during the study period.

Table 2: Comparison of outcomes among both the groups.

	Cord Milking	DCC	P-value
	Mean±SD	Mean±SD	
Ferritin at 6 weeks(ng/mL)	249.04±21.93	179.66±32.94	<0.001
Admission temperature(°C)	36.50±0.18	36.49±0.20	0.666
MAP 6 hours (mm Hg)	40.89±2.50	41.87±1.78	0.004
MAP 24 hours (mm Hg)	39.21±1.42	39.65 ± 1.27	0.036
Maximum serum bilirubin values (mg/dL)	11.99±1.36	12.12±1.29	0.497
Need for phototherapy	60 (71%)	55 (65%)	0.412
Grade I - IVH	14 (16%)	15 (18%)	0.838

DISCUSSION

There have been several studies on placental transfusion and hematological parameters in infancy. Many have included the preterm cohort.^{3,7,10}

The conventional testing at 6 weeks has been taken based on physiology of hemoglobin changes in preterm population which would have a physiological nadir around 4-8weeks of life and if authors could improve the iron stores around this crucial period it could translate to improved haemoglobin, which would also have an impact on neurodevelopment.¹¹⁻¹³

The method of cord milking used in our study was similar to that used in Kumar et al study.⁷ However the methods of cord milking varied across studies, while Hosono et al and Katheria et al milked 2-3times at a speed of 20cm/2sec.^{3,14} Rabe et al had same speed but performed 4 times, Alan et al milked 3 times at speed of 5cm/sec, March et al, Yadav et al, Bora et al milked 3 times with speed not reported.¹⁵⁻¹⁹

All the studies have milked the cord before clamping except Upadhyay et al, Kumar et al, Prateek et al that milked the cord 3 times after clamping.^{7,20,21} Authors chose the technique used by Kumar et al where the cord is clamped at a distance of 25 cm and only that segment of the cord is milked three times.

Hosono et al in their retrospective study reported that one-time umbilical cord milking after cord cutting had similar beneficial effects to multiple time umbilical cord milking before cord cutting in very preterm infants.²² Whether it would be ideal to milk the intact cord or milking after cord cut would be an area of future research. Recently, observational study by Hosono et al showed average amount of residual blood volume and blood volume per cm of cord as 15.5±6.7 (6-25) ml and 0.5±0.2 (0.2-08) ml/cm respectively and concluded that

infants could receive approximately 18 ml/kg of whole blood by one-time milking of 30 cm umbilical cord. With an average hematocrit of 40%, this volume is equivalent to approximately 13 ml of packed red blood cell transfusion (Hematocrit of 55%).²³ If authors assume the same conditions as done in study by Hosono et al our babies would have received additional 12.5ml (assuming 0.5ml per cm).

In the study, infants in the milking group had higher serum ferritin levels at 6weeks of life. Bora et al 2015 have studied iron stores of infants as long as 6 months of age and reported higher ferritin levels at 6months of age in infants who underwent umbilical cord milking of 40cm segment; however, this was in full term neonates.¹⁹ Serum ferritin normally decreases in first year of life. Few studies have reported pre-term infants <1,700 g with serum ferritin <50 ng/ml at 2 months predicts the risk of subsequent early-onset iron deficiency.²⁴ Upadhyay et al and Kumar et al have reported ferritin at 6weeks in preterm population (not requiring resuscitation) with cord milking.^{7,20} Authors have not taken in to consideration the maternal iron status as previous studies have clearly demonstrated that foetal iron stores are independent of maternal status and iron is accreted by foetus at a concentration gradient.²⁴

The speculative possibility of increased heat loss can be expected in preterm neonates if authors practice delayed cord clamping. Kaempf et al reported substantially significant higher normal delivery room temperature in their trial of DCC in preterm less than 35 weeks compared to ECC.²⁵ Recently Katheria et al in their trial on UCM in preterm reported higher normal temperatures in first five minutes of life.²⁶ This can be conjectured by increased transfer of warm placental blood. However, in this study there was no temperature differences among the two groups and this is reassuring in neonates with resuscitation where our primary focus is on temperature control.

In this study, neonates in milking group had lower mean arterial pressures at 6 hours and 24 hours of life but were within normal ranges, with no significant increase in need for inotropes with in first 48-72 hours of life. This finding of lower mean arterial pressures at 6hours of life is very important and is in correspondence with what authors normally expect a fall in blood pressure during the first 6 hours of life in extreme low birth weight before it starts to rise. This initial hypotension was described to be an IVH inducing factor.³ However, the incidence of IVH was lower in milking group but not statistically significant as the study was not powered for the secondary outcomes.

There have been contrarian reports in the literature where concerns were raised of increased hyperbilirubinemia in the neonates who received placental transfusion. The incidence of jaundice in both groups was similar in our study. Further, neonates in UCM group who required

treatment for hyperbilirubinemia did not have increased duration of phototherapy when compared to DCC group. This was supported by previous studies by Alan et al and Rabe et al.^{15,16} Only one trial, Kumar et al 2015 had reported increase in phototherapy days after umbilical cord milking.⁷ However, recent meta-analysis in 2015 have concluded no significant increase in jaundice with umbilical cord milking.²⁷

CONCLUSION

The studies demonstrate that umbilical cord milking results in better iron status among the preterm neonates as depicted by higher ferritin values at 6 weeks of age.

As speculated by various studies, there is no significant increase in the incidence of jaundice or need of phototherapy in the neonates who have underwent cord milking.

Thus, UCM is an effective placental transfusion strategy in preterm neonates to improve iron status that has a significant impact on neurodevelopmental outcome of the preterm cohort, with no significant adverse effects.

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