RESEARCH PAPER

Umbilical Cord Milking and Hematological Parameters in Moderate to Late Preterm Neonates: *A Randomized Controlled Trial*

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Objective: To investigate the effect of umbilical cord milking on hematological parameters at 6 weeks of age in late preterm neonates.

Design: Randomized controlled trial.

***Setting*:** A tertiary care center of Northern India during 2013-14.

Participants: 200 moderate to late preterm neonates randomly allocated to early cord clamping or umbilical cord milking group (100 in each).

Intervention: In milking group, 25 cm length of cord was milked towards the baby thrice after separating (within 30 s) it from placenta.

Main outcome measures: Hemoglobin and serum ferritin at 6 weeks of age.

Results: Mean (SD) serum ferritin [428.9 (217.6) *vs.* 237.5 (118.6) ng/mL; *P*< 0.01] and hemoglobin [12.1 (1.5) *vs.* 10.4 (1.2) gm/dL; *P*<0.01] at 6 weeks were significantly higher in umbilical cord milking group. In early neonatal period, hemodynamic and hematological parameters were not significantly different. Higher incidence of jaundice with higher phototherapy rates (33% *vs.* 9%; *P*<0.01) were noted in umbilical cord milking group.

***Conclusion*:** In preterm neonates, umbilical cord milking at birth enhances iron stores at 6 weeks of age. Higher phototherapy rates with this intervention are a matter of concern.

Keywords: *Anemia, Ferritin, Hemoglobin, Prematurity*.

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Delayed cord clamping, in which the cord is clamped only after a short delay (30 to 180 s) after birth, improves iron status, reduces anemia and need for blood transfusion, and also provides higher amount of placental stem cells to the infant without causing any harm to the mother [1,2]. Despite the evidence and recommendations for this intervention, there is reluctance by the neonatologists and obstetricians to adopt it because of possible conflict with immediate newborn resuscitation [3]. An alternative to this technique is umbilical cord milking, which is also a process of transferring extra blood from umbilical cord to the baby by milking or stripping the umbilical cord towards the baby. Recent studies have demonstrated that it results in comparable increase in hemoglobin (Hb) in extreme premature and term neonates [4,5]. Considering insufficient data regarding use of umbilical cord milking in moderate to late preterm neonates, we designed this trial with the objective to investigate its effect on iron status at 6 weeks in moderate to late preterm infants.

Methods

This study was a single center randomized controlled trial, conducted at Department of Pediatrics and Obstetrics of a tertiary care institute in Northern India from September 2013 to August 2014. Trial was approved by the Institutional ethical committee. Informed written consent was taken before the delivery from expectant mother and/or her spouse while mother was in labour room or Operation theater. Moderate to late preterm neonates (32 0/7 to 36 6/7 weeks) delivered either vaginally or by lower segment cesarean section at our institute and families living within 5 km radius of institution premises were included in the study. Gestational age was determined by last menstrual period (LMP) and by ultrasound of first trimester, if LMP was not known. Neonates were excluded if they had umbilical cord length less than 25 cm, or were non-vigorous at birth. Multiple births (twins, triplets), those born to Rh negative or retrovirus positive mothers, hydrops fetalis and those with major congenital anomalies, cord prolapse or cord anomalies like true knots were also excluded. Babies born to mothers with complications such as placental abruption, placental implantation disorders (placenta previa or accreta) or chorioamnionitis were excluded only if they were born limp.

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The sample size was based on a previous trial done in our institute which showed mean (SD) hemoglobin level in the intervention arm as 11.9 (1.6) g/dL and in the control arm as 10.9 (1.0) g/dL, respectively [5]. To detect a mean increase in hemoglobin by 1 g/dL in neonates with umbilical cord milking, the sample size in each group was estimated as 85 for a two-tailed value of 0.05 and power of 90%. Considering a 15% attrition rate, the total sample size was upscaled to 100 babies in each group. We used an online generated random number list, and assigned even numbers to early cord clamping (control) group and odd numbers to milking of cut cord (intervention) group. The numbers were written on small slips and placed in serially numbered opaque sealed envelopes. Sealed envelope was opened by a delivery room staff nurse, just after the delivery after ensuring baby is not limp and had no true knot. Standardized protocol for execution of each intervention was followed where all members of neonatal care team including obstetricians involved in this study were trained through separate live demonstrations for each intervention. Cord milking was also demonstrated with an online video [6]. In UCM (Intervention) group, just after delivery, umbilical cord was clamped and cut immediately (within 30 s) at placental end leaving cord length of at least 25 cm from the umbilicus of the baby. Attending neonatologist placed the infant under radiant warmer where cord was held upright and milked thrice towards baby at a speed of 10 cm/s, and then clamped at 2-3 cm from umbilicus. In control group, cord was clamped and cut immediately at 2-3 cm from umbilicus. The neonatal resident recorded the time elapsed by a wall-mounted clock in delivery room. If this co-ordination of delivery and assessment for inclusion took 30 sec or more, babies were excluded. Similar standard care was provided in both the groups. As per our obstetric department protocol, oxytocin was routinely given soon after delivery. It was given intramuscular in vaginal and intravenous in cesarean deliveries.

Relevant maternal details were obtained from case records. All enrolled infants were connected to a multi-parameter monitor and relevant data were collected by team leader who attended the delivery and subsequent data were collected at designated time by the doctor in neonatal intensive care unit. Infants were followed up at 6 weeks of postnatal age. Primary outcomes were hemoglobin and serum ferritin at 6 weeks of age. The secondary outcomes were: hemodynamic parameters (heart rate, respiratory rate and mean blood pressure), clinical parameters (respiratory distress, need for oxygen, polycythaemia and jaundice requiring phototherapy) and laboratory parameters (hemoglobin and hematocrit at 12 h and 48 h and serum bilirubin level at 48 h). Hemoglobin was measured by Cyan method while serum ferritin was measured by one step enzyme immunoassay sandwich method with a final florescent detection using ferritin kit (Biomeriux India).

Analysis of continuous data was done by unpaired t test and categorical data was compared using chi square or Fisher exact test as applicable. *P* value of less than 0.05 was considered significant. Analysis was done using STATA 11.0 software.

RESULTS

Fig.* 1** shows the flow of study participants. Out of 200 enrolled neonates, 177 completed the trial. Baseline characteristics in two groups were comparable (Table* I**) except maternal Hb which was more in intervention group by 0.3 mg/dL. The mean (SD) serum ferritin and hemoglobin at 6 weeks were higher in the intervention group as compared to control group (***Table* II**, ***Fig.* 2**). Mean blood pressure at 30 min, 12 h and 48 h after birth was higher in intervention group, but was not statistically significant (***Table* III**). In immediate neonatal period, hemoglobin and hematocrit were slightly higher in intervention group, but it was not statistically significant (***Table* III**). No significant difference was observed in heart rate and respiratory rate between two groups. Serum bilirubin level at 48 h was significantly higher in intervention group with significantly higher phototherapy rates (33% *vs.* 9%; $P<0.01$). In two babies in intervention group, serum bilirubin reached closed to exchange blood transfusion level but improved with intensive phototherapy without any complication. Ten infants in intervention group and five infants in control group developed respiratory distress, and required oxygen and admission in Neonatal Intensive Care Unit (NICU).

DISCUSSION

This study demonstrated that in moderate to late preterm neonates, umbilical cord milking improved hematological parameters (hemoglobin and ferritin) in early infancy. There was concern about higher incidence of jaundice requiring phototherapy in milking group. No other significant adverse effects were noted with umbilical cord milking.

The main limitation of the study was that it was an open-label trial as blinding was not possible because of the nature of two interventions. For hemodynamic monitoring, only vital parameters like heart rate, respiratory rate and BP was measured. Circulating volume was not measured as it was not feasible in our settings. A short duration of follow up was also one of the limitations.

Many trials have demonstrated the benefits of either delayed cord clamping and/or umbilical cord milking on

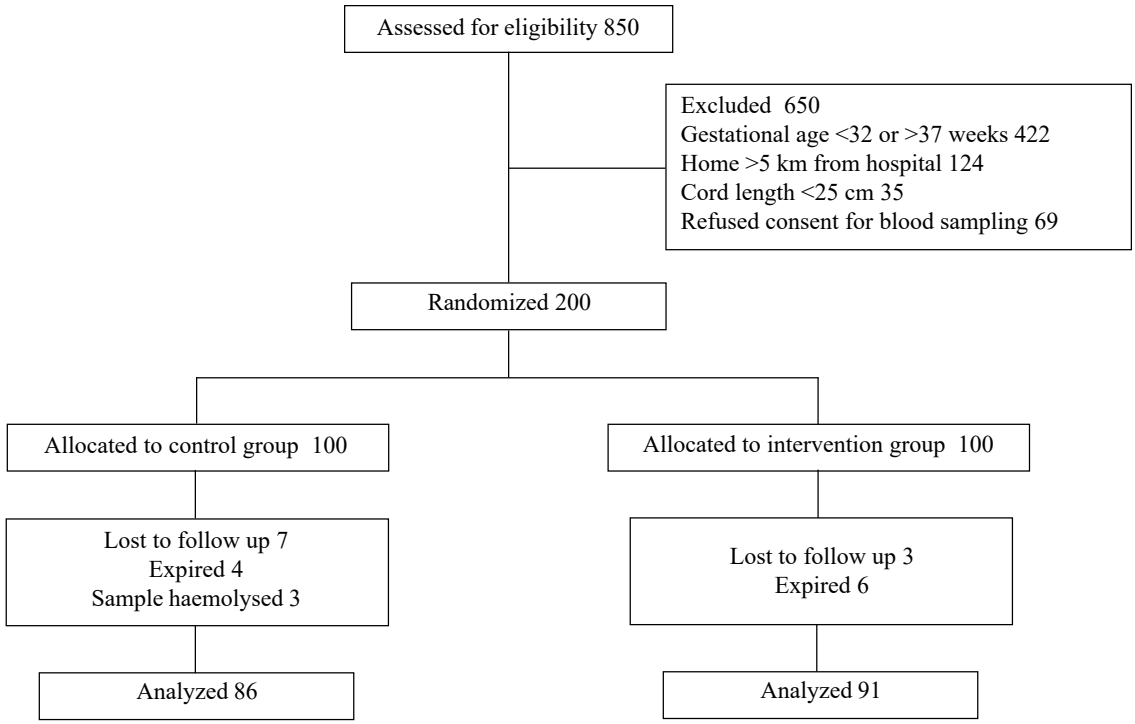

FIG. 1 *Flow of participants in the study.*

TABLE I BASELINE CHARACTERISTICS IN TWO STUDY GROUPS

Characteristics	*Early cord camping group*	*Umbilical cord milking group*	*95% CI of difference*	*P value*
Maternal				
Hemoglobin (g/dL)	9.5 (0.9)	9.8 (1.0)	0.01 to 0.5	0.04
Weight (kg)	62.9 (3.7)	63.5 (4.7)	63.8 to 62.6	0.29
Smoking[a]	14 (14%)	12 (12%)	—	0.67
Gestational age (wk)	34.5 (1.5)	34.7 (1.3)	0.2 to 0.6	0.29
Mode of delivery [a](Vaginal)	61 (61%)	56 (56%)	—	0.47
Use of oxytocin [a]	100 (100%)	100 (100%)	—	1
Neonatal				
Birth weight (g)	2354 (274)	2397 (268)	33 to 118	0.27
Sex (male) [a]	54 (54%)	52 (52%)	—-	0.78
APGAR Score at 1min	6.9 (0.3)	6.9 (0.3)	6.9 to 6.8	0.82
Small for gestational age [a]	10 (10%)	8 (8%)	—	0.62
Exclusive breastfeeding rates at 6 wk [a]	55 (63.9%)	55 (60.4%)	—	0.63
Weight at 6 wk (g)	3239 (244)	3291 (179)	12 to 114	0.11

Value in mean (SD) or [a] No. (%).

the hematological status immediately after birth which persists into early infancy [4,5,7-11]. In view of various studies and a Cochrane review [12] demonstrating the benefits of delayed cord clamping, delayed cord clamping has almost become a standard of care. However, it may not be feasible in all deliveries, especially in neonates who require resuscitation at birth. Umbilical cord milking also increases the placental and cord blood transfusion to the newborn, and is feasible even in those requiring resuscitation. Hosono, *et al*. [13]

TABLE ÌI COMPARISON OF HEMATOLOGICAL PARAMETERS IN TWO STUDY GROUPS

Parameters	*ECC Group (n=100)*	*UCM Group (n=100)*	*95% CI of difference*	*P value*
Hemoglobin (g/dL)				
12 hr	16.0 (2.7)	16.7 (2.3)	0.02 to 1.4	0.04
48 hr	15.4 (2.7)	15.6 (2.7)	0.7 to 0.9	0.67
6 week	10.4 (1.2) (*n*=86)	12.1 (1.5) (*n*=91)	1.3 to 2.1	<0.001
Packed cell volume (%)				
12 hr	48.2 (8.2)	50.1 (6.9)	0.2 to 4.0	0.07
48 hr	46.5 (7.2)	47.1 (7.7)	1.5 to 2.7	0.58
Serum ferritin (ng/mL) at 6 wks.	237.5 (118.6) (*n*=86)	428.9 (217.6) (*n*=91)	139.1 to 243.9	<0.001
Serum bilirubin at 48 hr	8.7 (2.5)	13.0 (3.5)	3.5 to 5.2	<0.01

Values in Mean (SD); ECC: early cord clamping; UCM: umbilical cord milking.

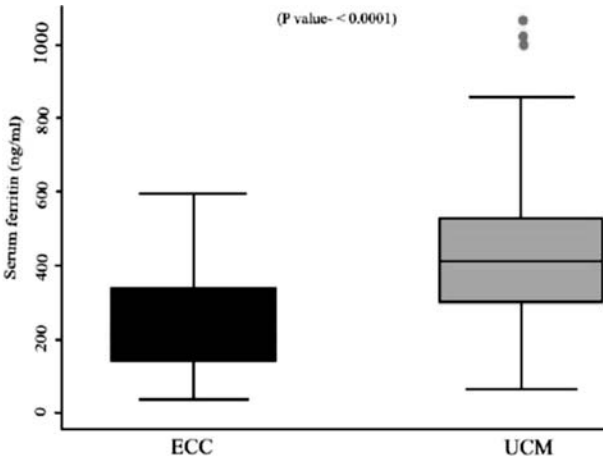

FIG. 2 *Box and Whisker plot for serum ferritin levels at 6 weeks.*

reported the first randomized controlled trial on 40 very preterm infants (26-29 weeks), and demonstrated higher hemoglobin, decreased number of transfusions and shorter duration of ventilation or supplemental oxygen in the milked group as compared to early cord clamping. A randomized controlled trial from our center on 200 term babies also reported that umbilical cord milking after birth leads to higher hemoglobin and better iron status at 6 weeks of age as compared to infants who received early cord clamping [5]. Earlier studies [8,13,14] evaluated milking while the baby was still attached to placenta, while we have milked the cord after cutting it leaving 25 cm length. The transfer of blood to the infant in this procedure may not be the same as that when cord milking is done with placenta still attached. However, there is no trial evaluating this comparison. Nakagawa, *et al.* [14] have earlier reported increase in incidence of jaundice requiring phototherapy in neonates who received delayed cord clamping. Another recent study [16] reported significantly longer duration of phototherapy with delayed cord clamping. Some other trials in term babies

TABLE III HEMODYNAMIC OUTCOME VARIABLES

Parameters	*ECC Group (n =100)*	*UCM Group (n =100)*	*95% CI of difference*	*P value*
Mean blood pressure (mmHg)				
30 min	48 (10.2)	50 (11.4)	0.9 to 5.1	0.18
12 h	48 (9.5)	49 (10.4)	1.8 to 3.7	0.49
48 h	47 (9.6)	48 (10.1)	2.4 to 3.1	0.79
Heart rate				
30 min	147 (10.1)	149 (12.7)	1.7 to 4.7	0.36
12 h	146 (10.3)	148 (13.4)	1.6 to 5.9	0.29
48 h	145 (11.7)	147 (13.7)	1.9 to 5.1	0.38
Respiratory rate				
30 min	50 (8.5)	52 (10.2)	0.7 to 4.6	0.14
12 h	49 (9.1)	51 (10.4)	1.1 to 4.4	0.23
48 h	48 (9.9)	49 (11.2)	1.9 to 3.9	0.49

Values in Mean (SD); ECC: early cord clamping; UCM: umbilical cord milking.

WHAT IS ALREADY KNOWN?

- Delaying of cord clamping at birth improves hematological parameters in infancy. Umbilical cord milking also has the potential to improve hematological parameters by transfer of more blood from placenta to the infant.

WHAT THIS STUDY ADDS?

- Umbilical cord milking helps in improving hematological status at 6 weeks of postnatal life in moderate to late preterm neonates.

have not shown increase in serum bilirubin or need for phototherapy [5,7,17]. This could be due to inability of relatively immature liver in late preterm to handle the extra blood transfused through these maneuvers.

We conclude that in moderate to late preterm babies, umbilical cord milking improves hematological parameters at 6 weeks postnatal age, but there seems to be a higher need for phototherapy with umbilical cord milking. Umbilical cord milking may be considered in moderate to late preterm neonates as a routine or in settings where delayed cord clamping is not feasible or when the neonate is likely to require resuscitation at birth.

Contributors: BK and PJ collected, analyzed and interpreted the data for the study, and drafted the manuscript. AU, SG, VJ and KD conceptualized and designed the study, analyzed the data and revised the manuscript. AU, SG, VJ and KD cross checked the data and helped in review of literature. Critical review and final approval of manuscript was performed by all authors. AU will act as guarantor of the study.
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