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The impact of umbilical cord milking on hematological and clinical outcomes in preterm infants

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Abstract
Background: Global preterm birth rate 10% and rate is increasing who are at risk of many complications. Anemia of prematurity is one of the preventable complications. Umbilical cord milking is a method of placental transfusion which may help to improve hematological and clinical outcome in preterm babies.
Objective of the study: To evaluate the effect of umbilical cord milking in improving hematological and clinical outcome in preterm babies.
Methodology: This Randomized control trial study was conducted in the Department of Obstetrics and Gynecology and Department of Neonatology. Neonates born between 28 to 34 weeks were assigned to either umbilical cord milking or no intervention group according to a computer-generated randomized sequence. After delivery of a baby umbilical milking was done for two times. Then the cord was clamped close to umbilicus & cut accordingly. The main outcome measure was hematocrit level at 6 hours of age. Total serum bilirubin was measured at 48 hours of age or earlier if clinically jaundice appeared. Clinical outcome data (Systolic blood pressure, need of initial respiratory support, jaundice & need for phototherapy, IVH, necrotizing enterocolitis) were monitored until 3weeks of life or discharge which was earlier.
Results: After meeting all exclusion criteria 114 patients were able to complete the study. Among 114 preterm neonates 57 were umbilical cord milking group and 57 were no milking group. Baseline characteristics of mother and neonate were comparable between two groups. There was significant increase in hematocrit level (57.3±3.5 Vs 47.4±4.5, in cord milking group & non milking group, P less than 0.001 in cord milking group. This study showed significant reduction in need of blood transfusion in first week of life in cord milking group. It was 3.5% V 21.1% in Cord milking group & non-milking group (P less than 0.001). No significant difference found in need of supplemental oxygen but requirement of assisted ventilation was significantly lower in cord milking group (19.3% V 31.5% in cord milking & non milking group respectively, P value 0.024). No statistical differences were found on the incidence of jaundice, need of phototherapy, total serum bilirubin level, blood pressure, intraventricular hemorrhage & necrotizing enterocolitis.
Conclusion: Umbilical cord milking increases hematocrit levels in preterm babies. Newborn who received cord milking, needs less number of blood transfusion and need of assisted ventilation is less in cord milking group. But there is no significant difference in blood pressure, incidence of jaundice, need of phototherapy, intraventricular hemorrhage & necrotizing enterocolitis in cord milking & non milking group.

Keywords: Umbilical cord milking, hematocrit, preterm

Introduction
In Telangana 14 out of 100 babies are born prematurely before 37 weeks of pregnancy and rate is rising [1]. Global preterm birth rate is 10% [2]. Preterm birth complications are now the leading cause of death in newborns and accounts for 30% of all newborn deaths in Telangana [2]. One of the worldwide public health obstacles in developing countries is anemia which is commonly found in young children and pregnant women. The evidences reveal that long-term ramification in cognitive brain effect comes from anemia during infancy and young children. When the umbilical cord is clamped immediately after birth, a significant amount of the fetal blood remains in the placenta leading to relatively lower red blood cell volume in the newborn.
Umbilical cord milking is a procedure in which clamped or unclamped umbilical cord is grasped and blood is pushed ("stripped") two times towards the newborn, in a rapid time

frame, usually within 10 seconds. The target of umbilical cord milking is to provide infants with their whole potential blood volume. Systematic reviews [3] have reported that delayed cord clamping (DCC), when compared with immediate cord clamping reduces the incidence of mortality, intraventricular hemorrhage (IVH), necrotizing enterocolitis (NEC) and need for blood transfusions in preterm infants. Hence, many professional organizations have endorsed delayed cord clamping as a standard delivery room practice for vigorous preterm infants [2]. However, delayed cord clamping could be difficult to implement in critically ill and apneic preterm infants in the delivery room needing resuscitation & there is a chance of hypothermia in preterm babies during delaying in cord clamping. Hence, umbilical cord milking has been investigated as a potential alternative to delayed cord clamping because resuscitative measures can proceed shortly after delivery. Umbilical cord milking improves pulmonary blood flow immediately at birth, assisting with lung expansion at the onset of respiration therefore facilitating earlier onset of breathing compared to delayed cord clamping [4]. The lack of benefit could reflect the lack of adequate placental transfusion during delayed cord clamping for infants delivered by LUCS. The American College of Obstetricians and Gynecologists statement acknowledges that there are limited data indicating whether delayed cord clamping performed during LUCS can improve placental transfusion [5]. Recent meta-analysis of 56 trials including 6852 preterm infants, umbilical cord milking was associated with lower odds of intraventricular hemorrhage. There was no significant difference between delayed umbilical cord clamping and umbilical cord milking for any outcome [6]. Another meta-analysis of 7 randomized controlled trials of umbilical cord milking in infants delivered at 33 weeks demonstrated that infants who undergo umbilical cord milking have higher hemoglobin (Hb%) and a lower risk for oxygen requirement at 36 weeks and intraventricular hemorrhage of all grades compared with those who undergo immediate cord clamping [7]. Recent study showed preterm neonates receiving umbilical cord milking had significant higher levels of hemoglobin (Hb), hematocrit, serum iron, lower prevalence of anemia and lower need for transfusions were noted in umbilical cord milking group [8]. Further evaluation of the effect of umbilical cord milking in improving the hematological & clinical outcome in preterm babies are needed.

Materials and Methods

Study design: This randomized controlled trial was done in the Department of Neonatology, after getting the approval from the Institutional Review Board.

Eligibility criteria

All inborn preterm neonates gestational age from 28 weeks to 34weeks were eligible for enrolment. Preterm neonates with congenital malformations, Rh- negative mothers and born to monochorionic multiple pregnancy were excluded from study.

Study procedure

This Randomized control trial was conducted in the Department of Neonatology, BSMMU, in collaboration with department of Obstetrics & Gynecology after approval by Institutional Review Board (IRB) over a period of one-year from May 2021 to April 2022.

Pregnant mothers anticipated to preterm delivery from 28 weeks to 34 weeks were eligible for this study. Women were enrolled at the onset of spontaneous labor (cut off point >7 cm cervical dilation) if they were in labor, or when the decision had been made for caesarean delivery for those not in labor. Preterm neonates with major congenital malformations & Rh-negative mothers were excluded from study. A written informed consent was taken from parents and assurance about confidentiality were given. Neonates born between 28 to less than 34 weeks were randomly allocated to either umbilical cord milking or non-milking group. Delivery attending doctors were trained about the procedure by hands on training & video demonstration. Attending doctor was made aware of the randomization by the researcher before delivery of the infant. In one group no intervention was done. In another group umbilical cord milking was done. After delivery of a baby umbilical cord was clamped away from the umbilicus keeping a distance about 25cm (about 10 fingers). Long segment of cord was milked toward the infant over two seconds duration each time by neonatal resuscitation team. Thus, milking was done for two times. Then the cord was clamped close to umbilicus & cut accordingly. Then routine umbilical cord care was ensured.

All required information for each neonate was recorded in a data collection form. The questionnaire was developed by reviewing evidence from books and scientific articles. The subjects were evaluated clinically & biochemically up to their hospital stay.

At 6 hours of age blood sample (1 mL) was taken in EDTA (ethylene diamine tetra acetic acid) tube. Hematocrit (Hct) level was assessed in clinical pathology department of BSMMU by fully automated blood cell counter (Sysmex, XN-2000 model, Japan). Different modes of respiratory support were initiated in patients following NICU protocol according to their respiratory severity score. Respiratory support was titrated according to infant's clinical condition, percent saturation of oxygen and arterial blood gas as per NICU protocol.

Blood pressure was measured by non-invasive oscillometric method in all neonates at 24 hours of age. Blood pressure calf was applied to the right upper extremity. Bladder length covered 75% to 80% (2/3rd) of arm circumference and bladder width was measured by measuring mid upper arm circumference. Three successive blood pressure readings were taken at 2- minute intervals. Final blood pressure was considered as the mean of three readings. The study neonates were clinically assessed for jaundice. Total serum bilirubin was measured at 48 hour of age or earlier if clinically jaundice appeared. 1ml of venous blood was sent in a tube. The bilirubin concentration was determined by using an automated diazo method in department of biochemistry. Requirement of phototherapy was decided as per unit protocol.

Necrotizing enterocolitis (NEC) was diagnosed clinically if any infant presenting with the triad of feeding intolerance, abdominal distension and gross bloody stool. Diagnosis was confirmed by abdominal Xray. Bell staging was used to classify necrotizing enterocolitis (NEC).

Bed side Ultra sonogram of brain was done by qualified radiologist or neonatologist of associate professor level to find out IVH (from grade I to IV) by 72 hour of age or any time if any clinical feature of IVH developed.

Data analysis

After collection, data were entered into a personal computer then edited, analyzed, plotted and were presented in graphs and tables. Qualitative data were expressed in proportion or percentage & statistical test were done by chi-square test and quantitative data were expressed as mean & SD and statistical test were done by student t test. All data were analyzed by SPPS software for windows, version20. P value <0.05 was considered as level of significance.

Results

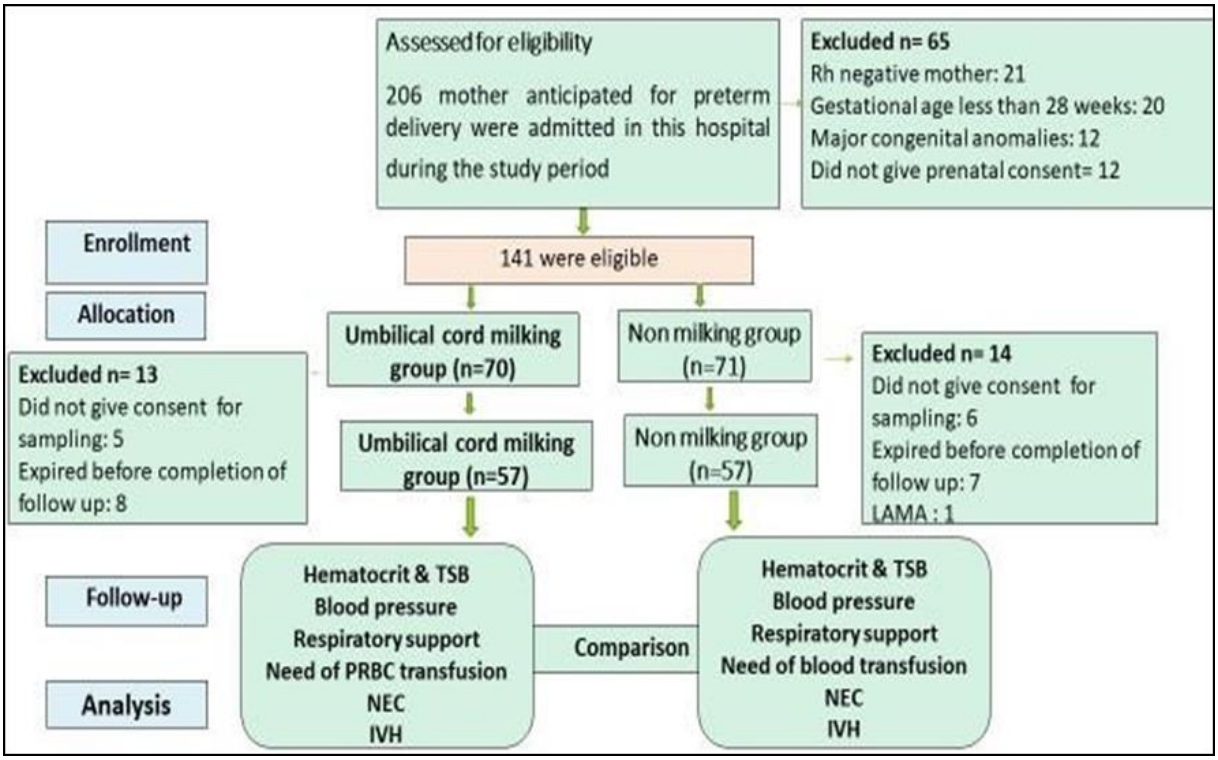

Fig 1: Consort flow diagram for patient enrolment and their outcome

A total of 206 mother anticipated for preterm delivery were admitted in this hospital during the study period who were eligible for this study. After delivery 65 newborns were excluded on basis of different exclusion criteria. Initially141 newborns were enrolled in this study & randomized to cord milking & non milking group. Out of them 114 patients were able to complete the study. Among 114 preterm neonates 57 were umbilical cord milking group and 57 were non milking group.

Table 1: Baseline characteristics of maternal factors (N=114)

Characteristics	Milking group (n=57)	Non milking group (n=57)	Total (N=114)	p –Value
Maternal age, n (%)				
21-30 yrs.	37 (64.9)	45 (78.9)	82 (71.9)	
31-40 yrs.	19 (33.3)	12 (21)	31 (27.2)	0.186 NS
>40yrs	1 (1.7)	0	1 (0.9)	
Parity, n (%)				
Primipara	26 (45.6)	28 (49.1)	54 (47.4)	0.708 NS
Multipara	31 (54.3)	29 (50.9)	60 (52.6)	
Antenatal visits, n (%)				
Less than 4	8 (14)	8 (14)	16 (14)	1.0 NS
4 or more	49 (86)	49 (86)	98 (86)	
Maternal DM, n%	6 (10.5)	9 (15.8)	15 (13.2)	0.406 NS
Maternal HTN, n%	20 (35)	17 (29.8)	37 (32.4)	0.746 NS
Oligohydramnios	20 (35.1)	21 (36.8)	41 (36)	0.845 NS
ACS	47 (82.5)	42 (73.6)	89 (78.1)	0.258 NS

Qualitative data are presented as number (percentage). Statistical test: Chi square test DM: Diabetes Mellitus, ACS: Antenatal corticosteroid, HTN: Hypertension. General characteristics of mothers are shown in Table 1. Baseline characteristics comparable between two groups. Most of the mother were in age group 21 to 30 years. There was no statistically significant difference in parity of mother, maternal morbidities, antenatal visit & antenatal corticosteroid.

Table 2: Baseline characteristics of neonates (N=114)

Characteristics	Milking group (n=57)	Non milking group (n=57)	Total (N=114)	P Value
Gestational age, n (%)				
28 to less than 32 weeks	16 (28.1)	17 (29.8)	33 (28.9)	0.836^{ns}
32 to 34 weeks	41 (71.9)	40 (70.2)	81 (71.1)	
Mean GA (weeks), Mean ± SD	32.5±1.8	32.6±2	32.55±1.9	
Birth weight, n (%)				
1000 g-1499 g	29 (50.8)	24 (42.1)	53 (46.5)	0.148^{ns}
1500 g-2499 g	26 (45.6)	32 (56.1)	58 (50.9)	
2500 g-4000 g	02 (3.5)	01 (1.8)	03 (2.3)	
Mean BW(g), Mean ± SD	1513±440	1607±453	1560±446	
Fetal growth, n (%)				
SGA	21 (36.8)	13 (22.8)	34 (29.8)	0.076ns
AGA	34 (59.6)	44 (77.2)	78 (68.4)	
LGA	2 (3.5)	0	02 (1.8)	
Gender, n (%)				
Male	36 (63.2)	24 (42.1)	60 (52.6)	0.024^{s}
Female	21 (36.8)	33 (57.9)	54 (47.4)	
Mode of delivery, n (%)				
LUCS	54 (94.7)	49 (86)	103 (90.4)	0.113ns
VD	3 (5.3)	8 (14)	11 (9.6)	
Resuscitation needed, n (%)	3 (5.3)	4 (7)	07 (6.1)	0.696ns
Intubation in delivery room	1 (1.8)	0	1 (0.9)	0.315ns
APGAR score at 5th min n (%)				
Excellent condition (7-10)	56 (98.2)	54 (94.7)	110 (96.5)	0.309ns
Moderately depressed (4-6)	1 (1.8)	3 (5.3)	04 (3.5)	

Qualitative data are presented as number (percentage). Statistical test: Chi square test

Quantitative data are presented as Mean ± SD. Statistical test: Student T test

GA: Gestational age; SGA: small for gestational age; AGA: Appropriate for gestational age; LGA: Large for gestational age**;** BW: Birth weight, LUCS: Lower Uterine Cesarean Section; VD: Vaginal delivery

Table 2 describe baseline characteristics of neonates comparable between two groups. Mean gestational age (weeks) was 32.5±1.8 Vs 32.6±2 in milking & non milking group respectively. Birth weight was mostly between 1000 gm to 2499 gm in both the groups with a mean birth weight (gram) 1513±440 Vs 1607±453 in milking & non milking group respectively. Most of the babies were AGA in both the groups. In cord milking group 36.8% was SGA and in non-milking group 22.8% was SGA. Gender distribution reflected male predominance. Most of the infants were born by LUCS. Resuscitation needed 5.3% babies in cord milking group & 07% babies non milking group. Only one baby of cord milking group was intubated in delivery room.

Table 3: Comparison of haematological outcomes between the milking group and non-milking group (N=114)

Characteristics	Milking group (n=57)	Non milking group (n=57)	p-Value
Haematocrit (%), Mean ± SD	57.3±3.5	47.4±4.5	.001^{s}
Blood transfusion 1st week, n (%)	2 (3.5)	12 (21.1)	0.001^{s}
TSB (mg/dl), Mean ± SD	9.8±2.7	8.9±2.5	0.86^{ns}

Quantitative data are presented as Mean ± SD. Statistical test: Student T Test Qualitative data is presented as number (percentage). Statistical test: Chi square test

Comparison of the hematological outcomes between the milking group and non-milking group is shown in Table 3.

This study showed significant increase in hematocrit level (57.3±3.5 Vs 47.4±4.5 in cord milking group & non milking group) in cord milking group. This study also showed significant reduction in need of blood transfusion in first week of life in cord milking group.

Table 4: Comparison of need of initial respiratory support between the milking group and non-milking group (N=114)

Characteristics	Milking group (n =57)	No milking group (n=57)	Total (N=114)	p-Value
Supplemental oxygen, n (%)	48 (84.2)	49 (86)	97 (85.1)	0.793ns
Assisted ventilation, n (%)	22 (38.5)	36 (63.2)	58 (50.8)	0.024^{s}
Mode of assisted ventilation, n (%)				
HHHFNC	0	1 (1.8)	1 (0.9)	0.049^{s}
CPAP	18 (31.6)	26 (45.6)	44 (38.6)	
MV	04 (7)	09 (15.8)	13 (11.4)	

Qualitative data are presented as number (percentage). Statistical test: Chi square test; HHHFNC: Heated humidified high flow nasal cannula; CPAP: continuous positive airway pressure; MV: Mechanical ventilator.

Comparison of need of initial respiratory support between the milking group and non-milking group is shown in Table 4. No significant difference found in need of supplemental oxygen but requirement of assisted ventilation was significantly higher in non-milking group.

Table 5: Comparison of clinical outcomes between the milking group and no milking group (N=114)

Characteristics	Milking group (n=57)	Non milking group (n=57)	p-Value
Mean systolic BP (mmHg), Mean ± SD	43.8±3.9	43.7±3	0.895
Jaundice n (%)	48(84.2)	51(89.5)	0.406
Phototherapy needed n (%)	48(84.2)	51(89.5)	0.406
NEC, n (%)	06(10.5)	08(14)	0.568
IVH, n (%)	03(5.3)	05(8.8)	0.463

Qualitative data are presented as number (percentage). Statistical test: Chi square test Quantitative data are presented as mean & SD. Statistical test: Student T test

BP: blood pressure; NEC; necrotizing enterocolitis; IVH: Intraventricular hemorrhage

Comparison of the clinical outcome between the cord milking and non-milking groups is shown in Table 5. No statistically significant differences were found in systolic blood pressure, jaundice, need of phototherapy, NEC & Intraventricular hemorrhage.

Discussion

This randomized control trial study was conducted involving preterm neonates born in a tertiary care hospital. It was demonstrated that umbilical cord milking compared to non-milking group resulted in increased level of hematocrit level, decrease need for blood transfusion and decrease need have assisted ventilation. In this study participant selection criteria were preterm delivery who had either a vaginal or caesarian delivery. The study conducted by [9] only vaginal deliveries were included. In another study, they involved caesarean section [10]. All of the study showed significant higher level of Hematocrit in cord milking group but there was difference in mean value of Hematocrit. In this study, after delivery of a baby umbilical cord milking was done for two times. In previous research [11] the umbilical cord was milked three times. Mean hematocrit level of participant differed in both study and probably difference in procedure was responsible for this difference. Our study showed significant higher level of hematocrit in cord milking group. Previous study [11] supported this finding showing higher level of birth hemoglobin and hematocrit levels in cord milking group. Another study [10] showed cord milking results in placental transfusion in term infants at the time of elective caesarean section with higher hematocrit levels at 36 to 48 hours of age. Whereas our study compared preterm neonates between 28 to 34 weeks of gestational age delivered both via caesarean section or vaginal delivery; these differences in gestational age and modes of delivery may account for the difference in study findings. Study done by [8], neonates receiving cord milking had significant higher levels of hematocrit in preterm babies below 34 weeks of gestation. This study showed newborn who received cord milking, needed less number of blood transfusion. In a systematic review [12] it was seen cord milking, when compared with immediate cord clamping, reduced the need for packed RBC transfusions. In fact, a vast majority of research found delayed umbilical cord clamping is effective in preventing the occurrence of anemia. With this concern, it should be reminded that preterm babies are exposed to the risk of anemia. They do not enjoy sufficient iron as a term infant does. The importance of iron insufficiency lies not only in the fact that it leads to anemia, but also in its adverse effects on child behavior and cognition [13]. The greatest barrier to the clinical application of placental transfusion is the long-held belief that over transfusion can lead to symptomatic polycythaemia and hyperbilirubinemia. In this study jaundice was found in both group but there was no significant difference. Research done by Erickson-Owens showed similar findings that there was no report of symptomatic polycythaemia and no significant differences between the immediate cord clamping and cord milking groups in the incidence of clinical jaundice, peak TSB levels, hyperbilirubinemia requiring hospitalization or readmission for phototherapy. But clinical symptoms including neonatal jaundice requiring a phototherapy were higher in the intervention group than the control in a study done by [11]. More recent study done by Sura *et al*. Jaundice was statistically significantly lower in umbilical cord milking compared to delay cord clamping. This study showed no significant difference between mean systolic blood pressure of both groups. But in another study, they showed significant rise in systolic blood pressure in cord milking group [11]. Our study did not show significant difference between intraventricular haemorrhage. But, in another study [11] umbilical cord milking significantly reduced the frequency of IVH. On the other hand, there was a statistically significantly higher rate of severe intraventricular hemorrhage in the umbilical cord milking group in study by [7]. They showed IVH was more common in extreme premature babies less than 28 weeks. In present study extreme preterm babies were excluded considering increased risk of IVH. This study did not show significant difference between necrotizing enterocolitis in both groups. Another study done by Nagano [14] also showed no significant difference in necrotizing enterocolitis. In this study, there was no significant difference in need of supplemental oxygen but significant difference in need of assisted ventilation. Literature evidence shows that cord milking immediately improves pulmonary blood flow and assists lung expansion at breathing onset [15, 16] Katheria *et al*. reached conclusions infants who had received cord milking, ongoing respiratory support were fewer in number than those who received immediate cord clamping.

Limitations

1. For USG of brain different sonologists were involved depending upon their availability.
2. Blood pressure could not be measured at exact time for all neonates.

Conclusion

Umbilical cord milking increases hematocrit levels in preterm babies. Newborn who receives cord milking, needs less number of blood transfusion and need of assisted ventilation is less in them.

But there is no significant difference in blood pressure, jaundice, need of phototherapy, intraventricular hemorrhage & necrotizing enterocolitis in cord milking & non milking group.

Recommendation

Umbilical cord milking can be a safe, feasible, inexpensive & less time-consuming way of placental transfusion in preterm babies in order to improve hematocrit level & ultimately to prevent anemia.

Conflict of Interest

Not available

Financial Support

Not available

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