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A Comparative Study of Placental Transfusion in Very Preterm Neonates

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Abstract: We aimed to compare the effect of Umbilical Cord Milking (UCM) and Early Cord Clamping (ECC) on haematocrit levels at 6weeks in very preterm neonates (28^{+1}weeks-31^{+6}weeks). Ours was a prospective comparative study comparing the haematological parameters and serum bilirubin values in early cord clamping (ECC) and Umbilical cord milking (UCM) and included 102 very preterm neonates over a period of 18months. Of the 102 very preterm neonates included in the study, 51 each were studied in early cord clamping and Umbilical Cord Milking (UCM). 30(29.4%) and 72(70.6%) neonates were in 28-29^{+6}weeks and 30-31^{+6}weeks respectively. 13.6% in ECC and 25.5% in UCM had risk factor of maternal anemia. In all 7 neonates with antepartum haemorrhage, ECC was the intervention done. Mothers with risk factor of gestational diabetes mellitus (GDM) were noted in 25.4% in ECC and 31.3% in UCM. Maternal infection was noted in 13.7% of the neonates in each group. 14.7% and 73.5% of very preterm neonates received one dose and two doses of antenatal steroid therapy respectively. Umbilical cord milking was done in 58.8% neonates delivered by normal vaginal delivery. ECC was the major intervention done in neonates with perinatal asphyxia. In neonates who required CPAP and mechanical ventilation, UCM was done in 38.2% and 2.4% neonates respectively. 27 neonates had Apgar score 1-4 and in 25 neonates early cord clamping was done. Male to Female ratio in UCM and ECC was 0.75:1 and 1.3:1. Mean haemoglobin and haematocrit at day 3 was high in neonates with UCM compared to ECC (16.57±2.34 vs. 15.71±2.17) and (50.34±7.07 vs. 46.21±6.55). Serum bilirubin levels were higher in UCM requiring phototherapy. Requirement of packed red cell transfusion (PRBC) in UCM was less compared to ECC (11.8% vs. 29.4%). Haemoglobin and haematocrit levels at 6 weeks were also high in UCM (12.16±1.85 vs. 10.47±1.71) and (36.71±6.1 vs. 31.57±5.10). Incidence of sepsis was less in UCM (13.7% vs. 19.6%). Haematocrit and haemoglobin at 6weeks were significantly higher and the incidences of anaemia lower in the UCM group. And the need for PRBC transfusion was found to be significantly less in UCM group. Need for mechanical ventilation and oxygen requirement were also significantly less for UCM group. Serum bilirubin at day 3 and requirement of phototherapy were significantly more in the UCM group compared to ECC even though none of the babies required exchange transfusion. No incidence of polycythemia was found in either group. There was no significant difference in incidence of sepsis in either group.

Keywords: Early cord clamping, Haematocrit, Very preterm neonates, Umbilical cord milking.

INTRODUCTION

Despite recent advances in perinatal and neonatal medicine that have improved the survival of very low birth weight infants, anemia of prematurity continues to complicate the care of these infants who often require red blood cell transfusions within the first three weeks of life [1]. PRBC transfusion remains the mainstay of management for the anemia of prematurity, but it is temporary and imperfect treatment, as its use inhibits erythropoiesis and comes with the risks such as infection, graft-versus-host disease and transfusion related lung and gut injuries. Current strategies to reduce the number of transfusions include the administration of recombinant human erythropoietin and supplementation with iron, folate and vitamin B 12. However these treatments have unclear benefits and accompanying risks[2-4].

Early cord clamping (ECC) is defined as clamping the umbilical cord within 30 seconds of delivery and is still the standard practise among the obstetricians especially in preterm infants. Delayed cord clamping (DCC), in which cord is clamped after a short delay improves iron status, reduces anemia, need for blood transfusion and provides higher amount of placental stem cells to the infant without causing any harm to the mother. A large body of evidence suggests that additional flow of blood from the placenta to the infant through DCC has several advantages to the newborn and does not result in harm. However, controversies exist over what constitutes the optimal time of DCC and the safety of this method when active resuscitation of the newborn is anticipated. Moreover, the delay in severing the umbilical cord might interfere with controlling maternal bleeding and suturing the uterine incision in caesarean delivery or the episiotomy or perineal tear in vaginal delivery.

An alternate to this technique is Umbilical Cord Milking (UCM). Umbilical cord milking (UCM) is a process of transferring extra blood from umbilical cord to the baby by milking or stripping the umbilical cord towards the baby [6]. Recent studies have demonstrated that it results in comparable increase in haemoglobin in premature neonates [7]. Milking cord helps minimize the time required for transfusion. A study by Rabe *et al.* [8] showed that cord milking is equivalent to delayed cord clamping in terms of outcomes. Milking is an easy procedure consuming less time and hence alleviating the concerns about the delay in the resuscitation. This method may be appealing in cases of anticipated birth asphyxia, given the importance of time in such situations. We can also speculate that pushing certain progenitor cells in some situations, such as autologous blood transfusion, is a subject of human trials in birth asphyxia [9].

One randomized controlled trial has compared DCC for 30 sec to cord milking in preterm infants and found that the two interventions resulted in a similar amount of placenta-fetal blood transfusion [8]. A recent study of cord milking compared with ECC in term infants by caesarean section showed as increase in haematocrit at 36-48hrs of age [11]. In one randomized controlled trial in extremely preterm neonates, reported that UCM reduced the need for red cell transfusions in the neonatal period [12].

Recent studies have demonstrated that it results in comparable increase in haemoglobin (Hb) in extreme premature and term neonates [6-7]. Considering insufficient data regarding use of umbilical cord milking in very preterm neonates, this study aims to investigate the effect of UCM on haematological status at 6weeks in very preterm neonates (28^{+1} to 31^{+6}weeks).

AIM AND OBJECTIVES

- To compare the effect of milking of the cord on haematocrit values in very preterm neonates at 6 weeks of age with early cord clamping.
- To compare the effect of milking of the cord on haematocrit and bilirubin levels at 3rd day of life with early cord clamping.

METHODOLOGY

This prospective comparative study was conducted over a period of 18 months and included very preterm babies admitted to neonatal intensive care unit of tertiary care hospital. Ethical clearance was obtained from Institutional Ethical committee.

Inclusion Criteria

All very preterm neonates (28^{+1}weeks to 31^{+6}weeks) born and admitted at neonatal intensive care unit of tertiary care hospital were enrolled into the study following informed consent from the parents.

Exclusion Criteria

- Monochorionic diamniotic twin pregnancy
- Severe intrauterine growth restriction in antenatal scans(<10th Centile)
- Known case of hydrops fetalis
- Known major congenital anomlies
- Cord prolapse and cord anomalies

Outcome

Incidence of anemia at 6weeks of life will be the primary outcome. Incidence of polycythemia, significant jaundice, need for resuscitation, perinatal asphyxia, number of blood transfusions, neonatal sepsis were secondary outcomes.

Grouping

All the eligible neonates will be allotted into 2 groups-Early cord clamping (ECC) and Umbilical cord milking (UCM).

MATERIALS AND METHODS

Informed written consent was taken before the delivery from the expectant mother and/or her spouse while mother was in labour room or operation theatre. The eligible babies were allotted into 2 groups-early cord clamping and umbilical cord milking. In our unit milking of cord and early cord clamping were routinely done depending upon the general condition of the baby. In the early cord clamping group, the cord was clamped immediately after delivery of the neonate. In umbilical cord milking group, the baby was placed near the mother's legs at or below the level of placenta for caesarean section and for vaginal delivery, the baby was held below the level of placenta. About 30cm length of the cord was held towards the placental side and cord was milked towards the baby at approximately 10cm/sec speed. The process was repeated three times, the cord was clamped and the baby handed over to the neonatal team. The haematocrit and bilirubin values

were measured at day 3rd of life and haematocrit was measured again at 6weeks of age. Data was collected using prepared questionnaire, by interview of parents, by physical examination of neonates, routine investigations done in the unit and monitoring for development of complications.

Definition of primary outcome variable

Anemia is defined as haematocrit below the normal for the age and birth weight-

Week	Premature neonates (1200-2500g)(g/dL)	Small premature neonates (less than 1200g) (g/dL)
0	16.4	16
1	16	14.8
3	13.5	13.4
6	10.7	9.7

Indications for transfusion include [13]:

A) Asymptomatic with haematocrit <21% and reticulocyte count <2%
B) Haematocrit >31% and hood oxygen <36% or mean airway pressure <6cm of H2O by CPAP
Or mechanical ventilation or apnea and bradycardia episodes requiring bag and mask ventilation while on caffeine therapy or tachycardia >100/min, tachypnea >80/min for 24hrs or weight gain <10g/day for 4 days on 100Kcal/kg/day.
C) Infants with haematocrit <36% and requiring >35% oxygen or mean airway pressure 6-8cm of H2O by CPAP/IMV

STATISTICAL ANALYSIS

Statistical analysis was done using SPSS 21. P values less than 0.05 were considered as statistically significant. Results on continuous measurements were presented on mean +/- SD. Results on categorical measurements were presented in number. Significance is assessed at 5% level of significance.

Sample size is calculated by formula

$$M = 2\sigma^2(Z_{1-\alpha} + Z_{1-\beta})^2 / (\mu_T - \mu_S - \delta)^2$$

δ : Superiority limit of the difference in means

μT: Mean of test treatment (12.1)

μS: Mean of standard treatment(10.4)

μT-μS: Expected mean difference

α: Significance level (0.05)

1-β: Power (0.90)

σ: Standard deviation(2.3)

The minimum sample size where the confidence limit is less than 0.05 is 39 subjects in each group. A total of 102 neonates were included in the study.

RESULTS

102 babies were enrolled in the study. 51 neonates in Early cord clamping (ECC) and 51 neonates in Umbilical cord milking (UCM). 30 neonates were in between 28-29^{+6}weeks and 72 were in between 30-31^{+6}weeks. Cord milking group has slightly higher incidence of maternal anemia (25.5% vs. 19.6%) compared to ECC, this had no statistical significance. 7(6.9%) mothers had antepartum haemorrhage (APH) of which all 7 belong to ECC. This implies that in mothers with antepartum haemorrhage early cord clamping was done, this has a statistically significance.

29 neonates had mothers with GDM, of which 13 had ECC and 16 neonates UCM done. This has no statistical significance. 14(13.7%) mothers had maternal infection of which ECC and UCM was done in 7 each. 90(88.2%) mothers received antenatal steroids of which 15(14.7%) received one dose and 75(73.5%) received two doses of steroids and UCM and ECC was done in 45 each. 48 (47.1%) neonates delivered by normal vaginal delivery, of which 30(58.8%) neonates underwent umbilical cord clamping. This has a statistical significance. The antenatal maternal factors in UCM and ECC is represented Table 1.

Table-1: Antenatal maternal parameters in ECC and UCC

Parameter	ECC N (%) 51(50%)	UCM N (%) 51(50%)	P
Gestational age			
28 –29+6weeks	20(39.2%)	10(19.6%)	
30-31+1weeks	31(60.8%)	41(80.4%)	0.030
Maternal Anemia	10(19.6%)	13(25.5%)	0.47
APH	7(13.7%)	0	0.01
GDM	13(25.5%)	16(31.4%)	0.51
Maternal Infection	7(13.7%)	7(13.7%)	1
Antenatal steroids			
One dose	10(19.6%)	5(14.7%)	
Two doses	35(68.6%)	40(73.5%)	0.3
Mode of Delivery			
LSCS	33(64.7%)	21(42.1%)	
NVD	18(35.3%)	30(58.8%)	0.017

APH= Antepartum haemorrhage, GDM=Gestational diabetes mellitus

Table 2: Neonatal characteristics

	ECC (n=51)	UCM (n=51)	P
Gender			
Male	29(56.9%)	22(43.1%)	0.16
Female	22(43.1%)	29(56.9%)	
Birth weight (gms)			
600-899	11(21.6%)	4(7.8%)	
900-1199	18(35.3%)	16(31.4%)	0.064
1200-1499	19(37.3%)	21(41.2%)	
1500-1799	3(5.9%)	10(19.6%)	
Apgar at 1min			
0-4	25(49%)	2(3.9%)	**0.001**
5-8	26(51%)	49(96.1%)	
Perinatal Asphyxia			
Yes	35(68.6%)	3(5.9%)	**0.001**
No	16(31.4%)	48(94.1%)	
Hemoglobin at day 3 (g/dL)			
10-14.9	10(19.6%)	6(15.7%)	
15-19.9	37(72.5%)	35(68.6%)	0.16
20-24.9	4(7.8%)	10(19.6%)	
Hematocrit at day 3(%)			
25-44.9	21(41.2%)	15(29.4%)	
45-54.9	23(45.1%)	22(43.1%)	0.18
55-64.9	7(13.7%)	14(27.5%)	
Hemoglobin at 6weeks (9g/dL)	19(37.3%)	4(7.8%)	
5-9.9	30(58.8%)	39(76.5%)	**0.001**
10-14.9	2(3.9%)	8(15.7%)	
15-19.9			
Hematocrit at 6weeks (%)			
<25%	40(78.4%)	20(39.2%)	
25-34.9%	8(15.7%)	24(47.1%)	**0.001**
35-44.9%	3(5.9%)	7(13.7%)	
PRBC transfusion			
Yes	15(29.4%)	6(11.8%)	0.02
No	36(70.6%)	45(88.2%)	
Serum bilirubin			
5-7.9	25(49%)	11(21.6%)	
8-10.9	14(27.5%)	20(39.2%)	0.014
11-13.9	12(23.5%)	20(39.2%)	
Neonatal jaundice			
Yes	16(31.4%)	35(68.6%)	**0.001**
No	35(68.6%)	16(31.4%)	
Phototherapy			
No	35(68.6%)	16(31.4%)	
1 Day	9(17.6%)	14(27.5%)	**0.001**
2 Days	5(9.8%)	12(23.5%)	
3 Days	2(3.9%)	9(17.6%)	
CPAP	20(39.2%)	30(58.8%)	**0.001**
Ventilation	39(76.5%)	3(5.9%	**0.001**

38 neonates had perinatal asphyxia during our study of which only 3 neonates had umbilical cord milking. 64 neonates had no asphyxia of which 48 neonates had UCM intervention done. 27(26.5%) neonates had Apgar at 1min between 0-4, of whom UCM was done in 2 and in 25 neonates ECC was done. 75(73.5%) neonates had Apgar score between 5-8, 49 neonates UCM was done. Only 2 neonates in cord milking group had Apgar score 0-4.

10(19.6%) neonates in UCM and 3(5.9%) neonates in ECC had birth weight >1500gms. 41

neonates in UCM had birth weight distribution of <900gms. 49 neonates in ECC group were <1500gms. Male to Female ratio in UCM and ECC was 0.75:1 and 1.3:1. CPAP requirement was seen in 59(57.8%) neonates of whom UCM was done in 39(38.2%) neonates and ECC in 20(19.6%) neonates. 33(32.4%) neonates required ventilation, UCM was done in only 3(2.4%) and 30(29.4%) neonates ECC was done.

Hemoglobin (Hb) at Day 3 of life: Mean Hb in ECC was 15.71±2.17, UCM was 16.57±2.34 and Mean of all neonates was 16.14±2.29. Distribution of Hb in both groups was shown in Table 2.

Hematocrit at Day 3: Mean haematocrit at day 3 in UCM and ECC was 50.34±7.07 and 46.21±6.55 respectively.

Serum bilirubin: Mean serum bilirubin levels in ECC and UCM were 8.75±2.06 and 10.53±1.819. This has a statistical difference between two groups. 35(68.6%) neonates in UCM and 16 (31.4%) neonates in ECC had developed neonatal jaundice requiring phototherapy, which has significant statistical difference. None of the babies required exchange transfusion. 6(11.8%)

Neonates in UCM required PRBC transfusion against 15(29.4%) in ECC, which has statistical significance implying cord milking reduced PRBC transfusion.

Mean Hb at 6weeks in UCM and ECC was 12.16±1.85 and 10.47±1.71. Mean Hematocrit at 6weeks in ECC and UCM was 31.57±5.10 and 36.71±6.1 respectively. 7(13.7%) in UCM and 10(19.6%) in ECC had culture positive sepsis. Neonatal characteristics are represented in table 2

DISCUSSION

This was a prospective comparative study to compare the haematological status of the early cord clamping versus milking of the umbilical cord in very preterm infants. Majority of the babies had gestational age of 30-31+6weeks. More babies in the gestational age of 30-31+6 weeks had UCM. Majority of the mothers were in the age group of 23-27years. The UCM group had slightly higher incidence of maternal anemia. For mothers with antepartum haemorrhage, early cord clamping was the most common intervention done. 31.4% of the babies born to mothers with GDM had underwent UCM against 25.5% of the babies born to mothers with GDM underwent ECC.

37.3% neonates had perinatal asphyxia of which, 68.6% underwent ECC and only 5.9% underwent UCM. 96.1% of the neonates had APGAR at 1min between 5-8 in UCM compared to ECC. Low APGAR at 1min (0-4) was found in 49% of ECC group. Katheria *et al.* [6] showed that there were no differences in Apgar scores, sex, and mode of delivery between ECC and UCM groups. Hosono *et al*. [12] reported higher 1 minute Apgar scores in infants who underwent UCM, whereas no difference in Apgar score at 1min was reported by March *et al*. [14].

The initial mean haemoglobin value in the milked group was significantly higher than in the control group (165(14g/l) s 141(16g/l), respectively, p<0.01) in a study by Hosono *et al*. [12]. Study conducted by March *et al*. [14] showed the neonates in the cord milking group had significantly higher initial haemoglobin and haematocrit levels than the neonates in the control group. In a study by Kilicdag *et al*. [15] on 3rd day haemoglobin for UCM was 16.8±2.7 and ECC was 16.3 ±2.4. The mean haemoglobin values, haematocrit levels and platelet counts were similar in both groups, except for the day 3 platelet count. Majority of the babies had a haematocrit values between 45-54.9%. More than 55% of the haematocrit values were found in 20.6% of the cases. Out of which 27.5% belong to UCM and 13.7% in ECC group. In the study by Bimlesh kumar *et al*. [16] in the immediate neonatal period, haemoglobin and haematocrit were slightly higher in intervention group (UCM) but it was not statistically significant. At 48hrs haematocrit was 46.5(7.2) in ECC and in UCM 47.1(7.7).

In a study by Prateek jaiswal and Upadhyay *et al*. [17] the mean haemoglobin and haematocrit level during the initial 48hrs of life in the UCM and ECC were comparable to the results obtained in previous studies. The neonates in the cord milking group had significantly higher initial haematocrit than the neonates in the control group in study done by March *et al*. [14].

Serum bilirubin levels were found to be higher in cord milking group. ECC group had more low levels of bilirubin values. 31.4% had bilirubin values between 11-13.9mg/dl out of which 39.2% belong to UCM group. There was not a significant increase in the need for phototherapy to treat hyperbilirubinemia in the cord milking group (91.7%) compared with the control group (97.4%). In the study by Bimlesh *et al.* [16] and Upadhyay *et al*. [18] serum bilirubin levels at 48hrs was significantly higher in UCM group with significantly higher phototherapy rates (33% vs 9%).

50% of the neonates developed neonatal jaundice out of which 68.6% belong to UCM group. 68.6% of the babies in UCM group received phototherapy when compared to ECC group. In case of duration of phototherapy 68.6% in ECC group do not received phototherapy at all compared to UCM group. 17.6% of UCM group do not receive intensive phototherapy compared to 3.9% in ECC group. None of the babies received exchange transfusion.

In our study 20.6% neonates received PRBC transfusion out of which 29.4% belong to UCM group. March *et al*. [14] hypothesized that UCM would result

in 30% reduction in the incidence of PRBC transfusion, which would yield an incidence of 49% in the treatment group. In their study UCM group, 83.3% of neonates required PRBC transfusion in the first 28days of life compared with 97.4% in the control group, yielding a RR of 0.86. Recent study by Song SY *et al*. [18] showed that UCM increased the initial haemoblobin levels and decreased the need for PRBC transfusion compared with ECC in neonates born between 24 and 33 weeks gestation. The mean number of transfusions in the milked group was significantly lower in delayed cord clamping group in the study by Hosono *et al*. [12]. Hemoglobin at 6weeks was found to be higher for the cord milking group when compared to ECC group. Majority neonates had haemoglobin values between 10g/dl -14.9g/dl. 37.3% of the ECC group had a haemoglobin values <10g/dl when compared to UCM (7.8%). 15.7% of UCM group has haemoglobin values >15g/dl when compared to ECC group (3.9%).

A RCT from Upadhyay's center [17] on 200 term babies reported that UCM after birth leads to higher haemoglobin and better iron status at 6weeks of age as compared to infants who received ECC. Rabe *et al.* [4] reported a higher haemoglobin values than reported by Upadhyay *et al*. [17] which was possibly related to the milking technique.

PCV at 6weeks was found to be higher for UCM group. 13.7% neonates in UCM group have PCV values more than 35% when compared to UCM group. Majority of the neonates did not develop sepsis. Out of 16.7% who developed sepsis 19.7% belong to ECC group. 58.8% neonates required mechanical ventilation of which 5.9% underwent UCM. In a Study by katheria *et al.* [2] showed that neonates receiving UCM require less resuscitation determined by less supplemental FiO2 and ventilation. In study by Hosono *et al*. [15], duration of ventilation or oxygen supplementation was less in UCM compared to ECC. Major limitations of the study are: small sample size, small duration of study, non-estimation of serum ferritin at 6weeks of life to assess iron stores in view of increased expenditure and randomised controlled trial would have been a better study in this setting.

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