Original Article

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Neonatology Section

Umbilical Cord Milking in Late Preterm Neonates and its Effects on Haematological and Haemodynamical Parameters-A Randomised Controlled Study

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ABSTRACT

Introduction: Delayed Cord Clamping (DCC) is a procedure, in which the cord is clamped after a short delay (30 s to 180 s) after birth. This improves iron status, reduce chances of anaemia and need for blood transfusion. However, DCC method compromised the success of resuscitation and induced various consequences, especially in neonates in need of emergency resuscitation. Umbilical Cord Milking (UCM), which is likewise a procedure of transporting additional blood from the umbilical cord to the newborn by milking or stripping the umbilical cord toward the baby, is an alternative to this approach. This study was conducted due to a lack of data on the use of umbilical cord milking in late preterm newborns.

Aim: To study the effect of UCM on haematological and haemodynamical parameters in late preterm neonates.

Materials and Methods: This single centre randomised controlled study was conducted, from November 2017 to August 2019 in the Department of Paediatrics, Kempegowda Institute of Medical Sciences, Bengaluru, Karnataka, India. Total 200 late preterm neonates fulfilling the inclusion criteria were randomised into cases (UCM group) and controls (Immediate cord clamping group). In UCM group, just after delivery, umbilical cord was milked towards the baby. In ICC group, cord was clamped and cut immediately. Primary outcomes included Haemoglobin (Hb), Haematocrit (Hct) and haemodynamic parameters (heart rate, respiratory rate and mean blood pressure), were noted at 48 hours of age. Clinical parameters (respiratory distress, need for oxygen, polycythemia and jaundice requiring phototherapy) were also noted. Student's t-test, Chi-square/fisher-exact test were used to find out the significance of study parameters.

Results: There was a significant higher Hb in UCM group (19.27±2.64 gm/dL) than Immediate Cord Clamping (ICC) group (16.32±2.09 gm/dL) with p-value=0.012 and higher Hct in UCM group (55.41±5.07%) than the ICC group (48.99±5.57%) with a p-value <0.001. Hence, there was higher placental transfusion in UCM group as shown by higher Hb and Hct in UCM group. There was also higher systolic, diastolic and mean blood pressure in the UCM group as compared to ICC group. Difference for mean arterial blood pressure was about 3 mmHg and was statistically significant (p-value <0.001). Hence, UCM leads to a higher mean arterial pressure at 48 hours of life.

Conclusion: Umbilical cord milking provides a greater placental transfusion, as demonstrated by higher Hb, higher Hct, higher blood pressure, and lesser requirement for inotropes and blood transfusions.

Keywords: Iron deficiency anaemia, Neonatal complications, Placental transfusion

INTRODUCTION

Anaemia is a one of common problems faced in infancy. It affects about 24.8% of world's population including developed as well as developing countries [1,2]. In India, the National Family Health Survey III showed that 70% of children below five years of age are anaemic [3]. Most cases of anaemia are due to iron deficiency. Worldwide, 50% of anaemia is caused by iron deficiency [4].

Cord Blood (CB) is a special product that is rich in Haemopoietic Stem Cells (HSCs); is used in the transplantation setting to repair haemopoiesis, and it corrects HSCs function in patients. It has been suggested that CB is rich in HSCs between 25 and 31 weeks gestation [5]. If the umbilical cord is clamped immediately after birth at 30 weeks of gestation, approximately one-half of the foetoplacental blood volume remains outside the newborn's circulation [6]. It has been reported that, in newborn animals, immediate clamping of the umbilical cord was reported to cause a decrease in blood volume of about 30-50%, compared to prenatal fetoplacental blood [7]. A safer, cost-effective and feasible intervention to reduce incidence of iron deficiency anaemia would be by 'placental transfusion'. Placental transfusion can be done by two procedures at birth: DCC and UCM/stripping [8].

In DCC, cord is clamped only after a short delay of 30 to 180 seconds after birth, allowing transfer of blood from placenta to the baby. It is known to improve haematological parameters in both preterm [9] and term infants [10]. The UCM also leads to comparable increase in Hb in both premature [11] and term infants [12]. Multiple systematic reviews revealed safety and efficacy of DCC between 30 seconds and 180 seconds [13]. However, compromised the success of resuscitation and induced underlying serious consequences, especially in neonates in need of emergency resuscitation. An alternative to this technique is UCM, which is also a process of transferring extra blood from umbilical cord to the baby by milking or stripping. Considering insufficient data regarding use of UCM in late preterm neonates, this study was undertaken to study the effect of umbilical cord milking on haematological and haemodynamical parameters in late preterm neonates.

MATERIALS AND METHODS

This single centre randomised controlled trial was conducted in the Department of Paediatrics, Kempegowda Institute of Medical Sciences, over a period of 21 months from November 2017 to August 2019. Parents were notified of the intervention and antenatal written consent was taken from either of the parents. Ethical Committee approval was taken to conduct the study (reference number: KIMS/IEC/D-41/2017).

Inclusion criteria: All neonates who were born between the gestational age of 35 weeks (245 days) and 37 weeks (258 days), newborns delivered vaginally or by caesarean section and neonates whose parents gave antenatal informed written consent were included in the study.

Exclusion criteria: Likewise multiple pregnancies, foetal hydrops; rhesus sensitisation, known major congenital abnormalities, length of umbilical cord milked <25 cm, babies with Appearance, Pulse, Grimace, Activity, and Respiration (APGAR) score <7, babies whose parents declined consent, placental or cord problems like abruptions, previa, accrete, increta, cord prolapse or true knots, babies in whom, coordination of delivery and assessment for inclusion took 30 seconds or more and Human Immunodeficiency Virus/Hepatitis B surface antigen (HIV/HBsAg) positive mothers were excluded from the study.

Sample size calculation: Sample size was calculated by the equation [12],

$4pq/d^2$, where prevalence p=28.5%,q=1-p (71.5%) and d=7

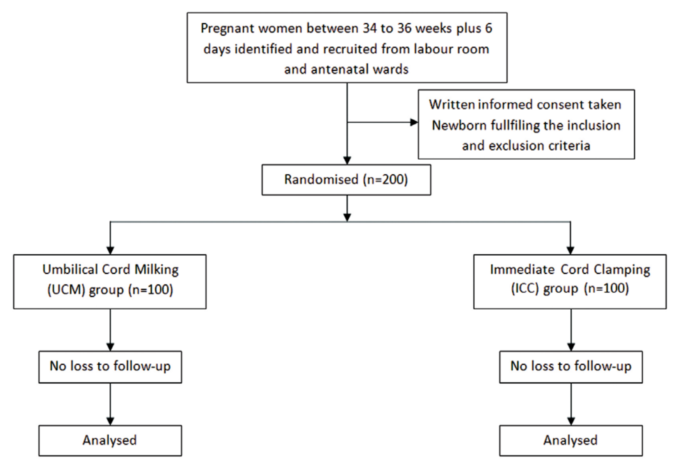
Hence, sample size=4×28.5×71.5/7×7=164.8 (approximated to 200)

Study Procedure

The gestational age was determined by Last Menstrual Period (LMP) and by ultrasound scan of first trimester if LMP was not known [14]. Pregnant women dated by their earliest ultrasound or LMP from 34 weeks to 36 weeks plus six days i.e., late pretem gestation were identified and recruited from the labour room and antepartum wards. A single neonatologist performed the procedure in all the babies.

Newborns were randomised into cases and controls using block randomisation technique comprising of 20 blocks each of size 10. Random allocation software version 1.0 was used to generate blocks. In this study, sealed opaque consecutively numbered envelopes were used for allocation concealment. Sealed envelopes were opened by the postgraduate student. In this way, the postgraduate did not know, whether newborn baby will go to the cases or control group. Data obtained was then, sent to the statistician.

The umbilical cord was clamped and severed at the placental end of the umbilical cord in the UCM (Intervention) group shortly after delivery, leaving a cord length of at least 25 cm from the baby's umbilicus [12]. The newborn was placed under a radiant warmer, where the cord was held upright and milked towards the baby for 30 seconds before being clamped at 2-3 cm from the umbilicus. The cord was clamped and severed at 2-3 cm from the umbilicus in the control group. The time since birth was recorded on the wall clock in the delivery room [Table/Fig-1].



[Table/Fig-1]: CONSORT chart.

Primary outcomes were Hb, Hct and haemodynamic parameters (heart rate, respiratory rate and mean blood pressure) at 48 hours of age. The secondary outcomes included: clinical parameters (respiratory distress, need for oxygen, polycythemia, necrotising enterocolitis, Intraventricular haemorrhage and jaundice requiring phototherapy).

STATISTICAL ANALYSIS

The statistical software namely Statistical Package for the Social Sciences (SPSS) version 22.0, and R environment version 3.2.2 were used for the analysis of the data. Microsoft word and Excel have been used to generate tables. Descriptive and inferential statistical analysis has been carried out in the present study. Results on continuous measurements are presented on Mean±SD (Min-Max) and results on categorical measurements are presented in number (%). Significance is assessed at 5% level of significance. The assumptions made on data were dependent variables should be normally distributed, samples drawn from the population should be random and cases of the samples should be independent. Student t-test (two tailed, independent) has been used to find the significance of study parameters on continuous scale between two groups (Inter group analysis) on metric parameters. Leven's test for homogeneity of variance has been performed to assess the homogeneity of variance. Analysis of Variance (ANOVA) test was also used for statistical analysis. The p-value=0.05 <p <0.10 was suggestive of significance, moderately significant (p-value: 0.01 <p ≤0.05) and strongly significant (p-value: p≤0.01).

RESULTS

In this study, 104 (52%) of neonates were females and 96 (48%) of neonates were males. So, study included marginally more number of female babies in both UCM and ICC group. The major mode of delivery was LSCS, more in both UCM group (58 deliveries-58%) and ICC group (59 deliveries-59%). Milked group had seven Small for Gestational Age (SGA) babies (7%) and ICC group had eight SGA babies (8%) and hence almost equal number of SGA babies was present in both groups. Haemoglobin will be low in small gestational age babies and effect of intervention will not be accurate. Haematocit is known to be higher in small gestational age babies. Nevertheless, distribution of small gestational age babies was almost equal in UCM and ICC group, and hence was not statistically significant. There was not much significance obtained on comparison of vital parameters in the two groups [Table/Fig-2].

Variables	UCM group	ICC group	p-value
Heart rate (bpm)	148.86±10.31	149.01±4.34	0.893
RR (bpm)	46.67±3.76	47.86±6.36	0.109
SpO_2%	97.14±8.83	97.98±0.35	0.342

[Table/Fig-2]: Comparison of vital parameters in two groups at 48 hours.
Student-t test
UCM: Umbilical cord milking; ICC: Immediate cord clamping; RR: Respiratory rate

For late preterm neonates 50^{th} centile for mean arterial blood pressure varies from 50 to 57 mmHg In the UCM group, systolic, diastolic and mean arterial blood pressures were higher as compared to ICC group [Table/Fig-3]. Difference for Mean Arterial blood Pressure (MAP) was about 3 mmHg and was statistically significant. Hence, UCM leads to a higher MAP at 48 hours of life in late preterm neonates.

Variables	UMC group	ICC group	p-value (Student's t-test)
Systolic blood pressure (mmHg)	73.90±5.00	72.20±5.25	**0.027**
Diastolic blood pressure (mmHg)	47.93±5.87	45.44±4.46	**0.001**
Mean arterial pressure (mmHg)	56.14±5.08	53.89±4.08	**0.001**

[Table/Fig-3]: Comparison of Non invasive blood pressure in two groups.

Most of the babies in the present study did not require any inotropes. Six babies required inotropic support. Four of these belonged to UCM group, hence milking will reduce the need for inotropes. Blood transfusion was given to six babies and four of them were from ICC group.

Haemoglobin estimation in UCM group was significantly higher with p-value=0.012 indicating statistically significant result [Table/Fig-4]. Mean Hb in UCM group was 19.27±2.64 gm/dL and in ICC group was 16.32±2.09 gm/dL. Red blood cells count in UCM group was 5.32±2.19 million/mm^3 and in ICC group was 4.11±3.10 million/mm^3 with p-value=0.002 which shows a strong correlation of higher RBC count in UCM group than ICC groups. Haematocrit in UCM group was statistically significant with p-value <0.001. Mean Hct of UCM group was 55.41±5.07% and ICC group was 48.99±5.57% with difference of about 5%, indicating milked group Hct was 5% higher.

Variables	UCM group	ICC group	p-value (Student's t-test)
Hb (gm/dL)	19.27±2.64	16.32±2.09	**0.012**
RBC (million/mm^3)	5.32±2.19	4.11±3.10	**0.002**
Haematocrit (%)	55.41±5.07	48.99±5.57	**<0.001**
Platelet (lac/mm^3)	2.36±0.77	2.54±0.79	0.102
Total count (c/mm^3)	12311.73±4048.91	11326.02±3902.51	0.081
MCV (fL)	101.15±8.15	98.23±11.06	**0.035**
MCH (pg)	34.72±2.41	34.24±2.57	0.174
MCHC (ug/dL)	33.32±3.30	36.99±30.09	0.227
Total bilirubin (mg/dL)	9.24±2.66	9.33±2.63	0.819
Direct bilirubin (mg/dL)	0.64±1.01	0.52±0.27	0.228

[Table/Fig-4]: Haematological parameters of two groups.
Hb: Haemoglobin; RBC: Red blood cells; MCV: Mean corpuscular volume; MCH: Mean corpuscular haemoglobin; MCHC: Mean corpuscular haemoglobin concentration

Exaggerated physiological jaundice was seen in 17% of UCM group and 18% of ICC group. Some of these cases had hyperbilirubinaemia and were given phototherapy. Transient Tachypnea of Newborn (TTN) was seen in 20% of UCM group and 13% of ICC group. Therefore, milking does not reduce risk of TTN in the present study study. An 8% of ICC group in the study developed respiratory distress syndrome whilst 1% of intervention group had Neonatal respiratory distress syndrome (RDS). Hence, milking in this study reduced that risk of development of RDS. A 7% of the babies in UCM group developed sepsis compared to 3% sepsis in ICC which might have led to increased risk for inotropes or blood transfusions. Two babies had NEC1A in UCM group. And one baby in ICC group had NEC1A [Table/Fig-5].

One of the babies belonging to UCM group had hyperbilirubinaemia requiring partial exchange transfusion. The baby was followed-up with repeat total bilirubin and direct bilirubin vales. These vales showed a progressively decreasing trend after the partial exchange transfusion.

Neonatal complications	UCM group (n=100)	ICC group (n=100)
Exaggerated physiological jaundice	17 (17%)	18 (18%)
Transient tachypnea of newborn	20 (20%)	13 (13%)
Respiratory distress of newborn	1 (1%)	8 (8%)
Sepsis	7 (7%)	3 (3%)
Necrotisingeneterocolitis1A	2 (2%)	1 (1%)
Dehydration	1 (1%)	0 (0%)
Partial exchange	1 (1%)	0 (0%)

[Table/Fig-5]: Neonatal complications distribution in two groups of patients studied.
p-value=0.395; ANOVA test.

DISCUSSION

When compared to ICC, this study shows that milking the cord in late preterm newborns results in greater HCT levels at 48 hours of age. It also demonstrated that UCM also had reduced risk of development of respiratory distress syndrome, lesser need for inotropes and blood transfusions and a higher mean arterial blood pressure. There was no increased risk of development of hyperbilirubinaemia/polycythemia. Only one baby with UCM had partial exchange transfusion due to polycythemia but overall incidence of polycythemia was not increased due to milking. A delay in cord clamping or milking the cord promotes placental transfusion by increasing wholeblood volume by 20 to 30% and red blood cell volume by 50 to 60% [15].

The newborn does not receive the additional blood volume from placental transfusion when the cord is cut quickly, resulting in a loss of 25 mg/kg of iron, or 33% less body iron [16]. This loss can deplete iron stores, putting the newborn at risk for anaemia and iron insufficiency during infancy [15,16]. In the infants with UCM, systolic, diastolic and mean arterial blood pressures were higher as compared to UCM group. Difference for mean arterial blood pressure was about 3 mmHg and was statistically significant. Hence, UCM leads to a higher MAP at 48 hours of life in late preterm neonates.

Cord milking appears to be a viable alternative to DCC, when timing is critical. In the study, it was found that milking the cord took <30 seconds and demonstrated significantly higher Hb and Hct levels at 48 hrs of age when compared with infants with ICC. These findings suggest that cord milking is easy to implement and takes only a few seconds to improve an infant's hematologic status. In a meta analysis involving 1912 infants, Hutton and Hassan, reported a slightly higher rate of asymptomatic polycythemia at 24 to 48 hrs of age with delayed clamping, but treatment was unnecessary and not associated with higher levels of jaundice and hyperbilirubinemia [17]. Another recent study conducted by McDonald SJ and Middleton P found no differences in the amount of asymptomatic polycythemia or clinical jaundice, but did report a small increase in jaundice requiring treatment although bilirubin levels were not reported [18].

In the study, there was no report of symptomatic polycythemia and no significant differences between the ICC and UCM groups in the incidence of clinical jaundice, peak TSB levels, hyperbilirubinemia requiring hospitalisation or readmission for phototherapy. In the study, not all infants included under the study had a TSB evaluation during the hospital stay.Of greater concern are the infants who are iron defificient and anemic in early infancy secondary to ICC. Similar to our study results in which almost half of the infants in the ICC group were anaemic at 36 to 48 hrs of age, Cernadas JMC et al., [19] found a higher incidence of anemia in the ICC group. Available evidence suggests anemia of infancy may contribute to neurodevelopment impairment [18]. There are no long term studies (>6 months) with follow-up of children with ICC, DCC or UCM. Examining the neurodevelopment of these children is a priority in light of the significant role iron has during the critical time of infant brain development.

In a study conducted by De Bernardo G ,DCC in patients born by elective caeserian section improved blood values,while it did not influence heart rate, SpO_2, temperature and glucose levels as compared with ICC group. Hence, DCC was considered in patients born by elective caesarean section as a valid practice by that study [20]. In another study conducted by Alavi A et al., it was found that UCM and delayed-clamping of the umbilical cord were effective in neonatal outcomes among preterm infants (28-34 weeks) and can be used as a well applicable method in hospitals to prevent he adverse effects of preterm birth [21], yet another study by Qian Y concluded that, DCC resulted in significant health benefits for term and preterm infants. The DCC was not associated with any clinically significant difference in the risk of postoperative haemorrhage, neonatal hyperbilirubinaemia or symptomatic polycythemia compared to early cord clamping [22].

In yet another study by Panbarana P et al., it was observed that both DCC and UCM have a comparable effect on haematologic status without deleterious effects on neonatal and maternal outcomes [23].

Although the present study was not powered to detect significant differences in neonatal morbidities like transient tachypnoea of newborn, necrotising enterocolitis and intraventricular haemorrhage between groups, we were able to find significant differences in the primary outcome variable and development of respiratory distress syndrome, need for inotropes and blood transfusion.

Cord milking is a low-cost intervention that accelerates placental transfusion. Placental transfusion appears to have an important role in enriching early infancy iron stores and assists in availability of iron for the developing brain [13]. Although DCC is the preferred method of transferring iron-rich blood from the placenta to the infant in the first few minutes after birth, it is not always feasible at the time of caesarean section/need for resuscitation. The UCM is a viable alternative.

Limitation(s)

Since the pertinent neonatal morbidities like necrotising enterocolitis, intraventricular haemorrhage have a low event rate in late preterm neonates, a very large sample size was needed to detect significant differences in these variables between UCM and ICC. Hence, main limitations of this study was the limited population size and the short time span included.

CONCLUSION(S)

The UCM provides a greater placental transfusion, as demonstrated by higher haemoglobin, higher Hematocrit, higher blood pressure, and lesser requirement for inotropes and blood transfusions. The UCM may reduce the incidence of respiratory distress syndrome. Hence, UCM may be preferable in late preterm infants, particularly in newborns when immediate resuscitation is needed. Although more larger trials are needed to confirm our observations, UCM should be considered as a beneficial option for late preterm infants.

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