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Original Article

Umbilical Cord Milking Reduces Duration of Inotrope Support in Preterm Infants Less than 32 Weeks of Gestation, Born with Cesarean Section in Comparison to Delayed Cord Clamping

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Abstract

Objective: Very preterm infants commonly need inotrope support. We aimed to demonstrate that umbilical cord milking (UCM) would reduce the need for inotropes in preterm infants born with cesarean section in comparison to delayed cord clamping (DCC).

Study Design: We compared the need of inotrope support, in a pilot randomized controlled trial, among preterm infants <32 weeks' gestation receiving UCM (n = 25) in comparison to those who underwent DCC (n = 24).

Results: Baseline maternal and newborn characteristics were similar. There was a significant reduction in the total duration of inotrope support (P = 0.004) and total duration of respiratory support (P = 0.021) in babies undergoing UCM when compared to those undergoing DCC. Trend toward reduction in incidence of hemodynamically significant patent ductus arteriosus and intraventricular hemorrhage was noted in UCM group.

Conclusion: UCM significantly improved respiratory and hemodynamic stability in preterm infants <32 weeks' gestation without associated complications.

Key words: Gestation, Infants, Preterm

INTRODUCTION

Delayed cord clamping (DCC) is beneficial for preterm infants. A systematic review (2012), on the timing of umbilical cord clamping in preterm infants, demonstrated that DCC was associated with fewer infants requiring transfusion for anemia, lower incidence of intraventricular hemorrhage (IVH) (all grades) as well as necrotizing enterocolitis when compared with immediate umbilical cord clamping. Peak bilirubin levels were higher in infants in the DCC group, but there was no statistically significant difference in the need for phototherapy between the groups.[1] Recent systematic review by Fogarty *et al*. found that DCC (>30 s) reduced hospital mortality and reduced proportions of infants receiving blood transfusion by 10%.[2] This growing body of evidence has led a number of professional organizations to recommend DCC in term and preterm infants.

An alternative to DCC is umbilical cord milking (UCM), in which the unclamped umbilical cord is grasped, and blood is pushed toward the infant several times before it is clamped. This procedure can be performed within 20 s. It has particular appeal for circumstances in which the 30–60-s delay in umbilical cord clamping may be too long, such as when immediate infant resuscitation is needed or maternal hemodynamic instability occurs.[3] A recent meta-analysis of UCM in infants delivered at <33 weeks

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demonstrated that infants who undergo UCM have higher hemoglobin (Hb) and a lower risk for oxygen requirement at 36 weeks and IVH of all grades compared with those who undergo immediate cord clamping (ICC).[4]

American College of Obstetricians and Gynecologists (ACOG) statement acknowledges that there are limited data indicating whether DCC performed during cesarean delivery (CD) can improve placental transfusion.

Aladangady *et al.* reported lower circulating red cell volume with DCC in neonates born by CD compared with vaginal delivery (VD). One could speculate whether more blood remains in the placenta when a neonate is delivered by CD because the anesthetic and surgical interventions interfere with the active contraction of the uterine muscles to expel the placenta.[5]

A recent study of 154 infants delivered by CD, 75 were assigned to UCM and 79 to DCC. Neonates randomly assigned to UCM had higher superior vena cava flow and right ventricular output in the first 12 h of life. Neonates undergoing UCM also had higher delivery room temperature, blood pressure over the first 15 h, and urine output in the first 24 h of life. There were no differences between the 43 infants delivered by VD.[6]

This is an area of active research, and several ongoing studies are needed to evaluate possible benefits of UCM compared with DCC, especially in babies born by cesarean section. Given that up to 90% of preterm infants are delivered by CD, there is a critical need to determine which therapy should be given to preterm infants delivered by CD.

Thus, this study is planned to evaluate whether UCM is better than DCC in reducing the need for inotrope support in very preterm infants born of cesarean section.

MATERIALS AND METHODS

Study Design

This pilot randomized controlled trial was conducted at Lokmanya Tilak Municipal tertiary care Hospital, Sion, Mumbai. The study was approved by the Institutional Review Board and was conducted between January 2018 and September 2018. The primary outcome needed for inotrope support within 24 h of delivery.

Objectives

The primary aim of the study was to determine, in comparison to DCC, whether UCM reduce the need for inotrope support in first 24 h of life, in preterm infants <32 weeks' gestation born of cesarean section. We also wanted to determine if UCM reduced the need for transfusions, respiratory support, and mortality in offspring without adding complications.

Population

Pregnant women of <32-week gestation (dated by last menstrual period or earliest ultrasound) and undergoing cesarean section delivery were identified from the antepartum unit and labor room. Parents were approached and informed written consent was taken to enroll their newborn for randomization in either group. Entry criteria included newborns with the gestational age of 26 0/7–31 6/7 weeks born by cesarean section. Exclusion criteria included newborns requiring resuscitation, monochorionic multiples, placenta previa, abruptions, Rh sensitization, hydrops, life-threatening congenital anomalies, HIV, and hepatitis B surface antigen positive mothers.

Mothers were randomly assigned just before delivery by opaque, sealed envelopes. The obstetricians were made aware of the randomization by the neonatology team before delivery of the infant. Dichorionic twins received the random assignment separately. Using the timer in the delivery room one member of the team recorded and counted out loud the time elapsed from when the infant was delivered until the time the umbilical cord was clamped by the obstetrician in both arms of the study. Neonates who did not cry immediately after birth were excluded and ICC was performed.

Sample Size Calculation

The sample size was calculated based on the incidence of the need for inotrope support among preterm infants (<32 weeks) born in the prior 2 months. Taking into consideration an incidence of need for inotrope support of 60% to achieve a reduction to 26%, 28 patients in each group would be necessary for an alpha error of 0.05.

Intervention

UCM was performed by holding the infant at or ~20 cm below the level of the placenta. The cord was pinched as close to the placenta as possible and milked toward the infant over a 2-s duration. The cord was then released and allowed to refill with blood for a brief 1–2-s pause between each milking motion. This was repeated for a total of 4 times. After completion, the cord was clamped, and the neonate was handed to the neonatal team. DCC was performed by holding the infant at or ~20 cm below the level of the placenta and waiting for 45 s before clamping the cord. In both arms, infants were wrapped in the sterile Polydrape without drying, with head covered and were taken to radiant warmer. Neonates were managed as per labor room protocol of temperature stabilization and respiratory support.

Blinding was achieved by allowing only investigator, fellows posted in labor room and the obstetrician performing the intervention, to be aware of the allocation arm. No documentation of the intervention was made in the indoor case paper. The randomization cards assigned a subject identification number was kept by the investigator. Blinded echocardiograms and head ultrasounds were performed by a trained research fellow.

Outcomes

Primary outcome needed for inotrope support in the first 24 h of life. Monitoring of skin temperature, hemodynamic parameters (heart rate, capillary refill time, non-invasive blood pressure, and perfusion index), and respiratory system parameters (respiratory rate, distress score, and saturations) was done every hour for 24 h of life. Infant was provided with respiratory support anytime in the labor room and neonatal intensive care unit (NICU) as required. Newborns were provided inotrope support if (1) capillary refill time was more than 4 s or (2) non-invasive blood pressure revealed systolic or diastolic arterial pressure of less than lower 95th percent confidence limit as per gestational age given by Zubro's charts. Time of starting inotrope, drug, and dose and duration of inotrope support were documented.

Early echocardiogram (at 12 h) was performed with the Sonosite ultrasound system for detection of hemodynamically significant ductus arteriosus. Repeat echo was performed at 12 hourly intervals till 72 h. Measures of ductal diameter (narrowest diameter before entering in the left pulmonary artery), direction of flow, left pulmonary end-diastolic velocity, and left atrial to aortic root ratio were documented. Patent ductus arteriosus (PDA) was treated if it was hemodynamically significant.

All neonates were screened for a bedside head ultrasound at 24, 72 h, and 7 days to document evidence of IVH and it was graded as per Volpe's classification. Hb and hematocrit were documented at birth. Repeat screen was done if required during the NICU stay. Septic screen was done if sepsis was suspected. Initiation of feeding and escalation of feeds were decided by the treating physician. Time to reach full enteral feeds was noted. Any incidence of feeding intolerance was documented. Necrotizing enterocolitis was labeled according to modified bell's criteria.

Baby was monitored for icterus, peak bilirubin levels were documented, ad treatment (phototherapy) was offered as per NICE guidelines. All babies were screened for retinopathy of prematurity starting at 21 days of life (as per unit protocol). The requirement of oxygen at 36 weeks corrected for gestational age (bronchopulmonary dysplasia) was noted.

Babies underwent screening ultrasound at 28 days of life for assessment of periventricular leukomalacia. Number of blood transfusions till discharge or death and volume received per transfusion were documented. Babies were followed until discharge or death.

Statistical Analysis

We performed statistical analyses using SPSS Statistics version 23. Normally distributed continuous outcome variables were compared with the unpaired Student's *t*-test, and nonparametric continuous outcome variables were analyzed with the Mann–Whitney *U*-test. We based our sample calculations on the basis of previous data collection. Two-sided $P < 0.05$ was considered significant.

RESULTS

The baseline maternal, fetal, and newborn characteristics of UCM and DCC groups are summarized in Table 1, which shows no significant difference between groups.

Baseline maternal and newborn characteristics were similar. There was a trend in reduction of the need for inotrope support in UCM group (12%) as compared to DCC group (33.3%) ($P = 0.073$) with significant reduction in total duration of inotrope support ($P = 0.004$) in UCM group. Although there was no difference in need for respiratory support, there was significant reduction in total duration of respiratory support in babies undergoing UCM when compared to those undergoing DCC ($P = 0.021$). Trend toward reduction in incidence of hemodynamically significant PDA (31% in UCM group and 45.8% in DCC group) was noted ($P = 0.096$). Furthermore, reduction of incidence of IVH (any grade) was found in UCM group (12%) than those undergoing DCC (33.3%), this difference was not statistically significant. There was no statistically significant difference in Hb at birth, temperature on admission to NICU, incidence of polycythemia, requirement of partial exchange, incidence

Table 1: Baseline maternal and neonatal characteristics

Parameters	UCM (*n*=25)	DCC (*n*=24)	*P*-value
Maternal age (years)	29±4	28±3	0.75
Gestational age (weeks)	30±2	30±2	090
Birth weight (g)	1315±274	1272±269	0.58
Sex (male)	13 (52%)	14 (58.3%)	0.437
Pregnancy induced hypertension (*n*, %)	6 (24%)	5 (20.8%)	0.531
Diabetes (gestational or pre-gestational) (*n*, %)	2 (8%)	2 (8.3%)	0.680
LPV (*n*, %)	6 (24%)	5 (20.8%)	0.531
Some antenatal steroids (*n*, %)	21 (84%)	16 (66.66%)	0.141

Data are presented as mean+SD or expressed in percentages. UCM: Umbilical cord milking, DCC: Delayed cord clamping

of feed intolerance, peak bilirubin level, total duration of phototherapy, incidence of necrotizing enterocolitis, sepsis, total duration of NICU stay, and final outcome of death or discharge [Table 2].

DISCUSSION

Neonatal Resuscitation Program, WHO, and ACOG recommend DCC (>30 s) for all preterm babies at birth. A systematic review (2012) on timing of umbilical cord clamping in preterm infants, defined DCC as a delay of more than 30 s, with a maximum of 180 s. DCC was associated with fewer infants requiring transfusion for anemia (relative risk [RR], 0.61; 95% confidence interval [CI], 0.46–0.81), lower incidence of IVH (RR, 0.59; 95% CI, 0.41–0.85) as well as necrotizing enterocolitis (RR, 0.62; 95% CI, 0.43–0.90) compared with immediate umbilical cord clamping. Peak bilirubin levels were higher in infants in the DCC group, but there was no statistically significant difference in the need for phototherapy between the groups. Recent systematic review by Fogarty *et al*. including 18 RCTs, 2834 infants, found that DCC (>30 s) reduced hospital mortality (RR 0.68; 95% CI 0.52–0.90) number needed to benefit being 33 also reduced proportions of infants having blood transfusion by 10%.[2]

Table 2: Clinical variables of preterm infants in the delivery room and the NICU

Parameter	UCM (*n*=25)	DCC (*n*=24)	*P*-value
Birth Hb–(g/dL)	17.1±1.6	17.8±1.8	0.168
Hct (%)	53.3±5.8	54.9±5.8	0.32
Temperature on admission (degree C)	36±0.5	35.9±0.5	0.58
Respiratory support–*n* (%)	13 (52%)	12 (50%)	0.558
Duration of respiratory support (hours)	39±84	185±279	0.021
Surfactant–*n* (%)	8 (32%)	7 (29.2%)	0.538
Need for inotrope support within 24 h–*n* (%)	3 (12%)	8 (33.3%)	0.073
Duration of inotrope support (hours)	5.76±19	51±30	0.004
Polycythemia (Hct >65%)–*n* (%)	2 (8%)	4 (16%)	0.314
Partial exchange–*n* (%)	1 (4%)	2 (8.3%)	0.484
Need for transfusion–*n* (%)	5 (20%)	6 (25%)	0.469
PDA–*n* (%)	6 (31%)	11 (45.8%)	0.096
PDA requiring treatment–*n* (%)	6 (31%)	10 (41.6%)	0.155
Any IVH–*n* (%)	3 (12%)	8 (33.3%)	0.073
Severe IVH (Grade 3 and with PVHI)–*n* (%)	1 (4%)	2 (8.3%)	0.484
Feed intolerance–*n* (%)	1 (4%)	3 (12.5%)	0.289
Peak bilirubin value–(mg/dl)	13.8±2	14.7±2	0.42
Duration of phototherapy (days)	4 (16%)	3 (12.5%)	0.645
NEC any grade–*n* (%)	1 (4%)	1 (4.1%)	0.745
NEC Grade 3–*n* (%)	0	1 (4.1%)	0.490
Time to reach full feeds (days)	4±4	7±5	0.12
Sepsis–*n* (%)	4 (16%)	7 (29.1%)	0.224
Discharge–*n* (%)	23 (92%)	23 (95.8%)	0.516
Duration of hospital stay (days)	24±3	28±3	0.763

Data are presented as mean+SD or expressed in percentages. PDA: Patent ductus arteriosus, Hct: Hematocrit, Hb: Hemoglobin, DCC: Delayed cord clamping, NICU: Neonatal intensive care unit, IVH: Intraventricular hemorrhage, PVHI: Periventricular hemorrhagic infarction, NEC: Necrotizing enterocolitis

An alternative to DCC is UCM. Meta-analysis of seven randomized controlled trials of UCM in infants delivered at <33 weeks (n = 501) demonstrated that infants who undergo UCM have higher Hb and a lower risk for oxygen requirement at 36 weeks and IVH of all grades compared with those who undergo ICC.[4]

Three trials of DCC that stratified by mode of delivery found no difference in hematocrit levels or tagged red blood cells in infants delivered by CD.[7-9] The ACOG statement acknowledges that there are limited data indicating whether DCC performed during CD can improve placental transfusion.

Rabe *et al*. randomly assigned 58 neonates born at <33 weeks' gestation to UCM (4 times) or to a 30-s delay in cord clamping. Although they did not find any differences in outcomes, the infants treated with DCC had a lower CD rate (58% vs. 78%).[10] Because a greater number of infants undergoing DCC were delivered by VD, the lower proportion of CD in this group may have reduced the difference seen between the two approaches.

Aladangady *et al*.[5] reported lower circulating red cell volume with DCC in neonates born by CD compared with VD. One could speculate whether more blood remains in the placenta when a neonate is delivered by CD because the anesthetic and surgical interventions interfere with the active contraction of the uterine muscles to expel the placenta.

A recent study of a total of 197 infants (mean gestational age 28 weeks). Of the 154 infants delivered by CD, 75 were assigned to UCM and 79 to DCC. Of the infants delivered by CD, neonates randomly assigned to UCM had higher superior vena cava flow and right ventricular output in the first 12 h of life. Neonates undergoing UCM also had higher delivery room temperature, blood pressure over the first 15 h, and urine output in the first 24 h of life. There were no differences between the 43 infants delivered by VD.[6]

Although there was no statistically significant difference in the primary outcome of need for inotrope support, our study demonstrated statistically significant reduction in total duration of inotrope (P = 0.004) and respiratory support (P = 0.021) with UCM compared with DCC.

Placental blood during UCM is directed toward the lungs during a time when there is a rapid fall in pulmonary

resistance, unlike any other period when volume is given which may have resulted in better respiratory transition. Pulmonary blood flow supplies most of the preload to the left ventricle improving left ventricular output providing hemodynamic stability which can explain reduction in need for inotrope support.

Although we did not see a statistically significant difference ($P = 0.073$) in IVH between groups, there is a definite trend in reduction of IVH in UCM (12%) versus DCC (33.3%). Because of improved hemodynamics in umbilical cord group during critical time period (<24 h), may prevent IVH from occurring by stabilizing the fluctuations in systemic blood flow that has been proposed as a mechanism for IVH. Lower incidence of hemodynamically significant PDA is also attributed to better respiratory transition and hemodynamic stability seen with UCM.

Studies have shown that low birth weight infants undergoing DCC are warmer than those undergoing ICC, possibly because of the warm placental blood entering the newborn.[11] An additional advantage for UCM is the rapid time frame for UCM to occur. Theoretically, this should not only allow a minimal delay of resuscitation but also should prevent hypothermia in the operative field. The difference between the two groups in our trial was only 25 s, and as the baby was transferred after stabilization of temperature in the labor room, there was no difference in admission temperature among the two groups. UCM allows rapid placement of the newborn under the radiant warmer.

An important limitation of our trial was the lack of an ICC group. Because both DCC and UCM provide a placental transfusion regardless of the mode of delivery, it was expected that we would not see substantial differences in clinical outcomes. Because the recommendations by ACOG demonstrated that DCC improved clinical outcomes, we did not have equipoise to randomly assign infants to a third group that did not receive a placental transfusion.

Despite the concerns that UCM may provide a rapid bolus of blood, our data are consistent with other studies that found that UCM is beneficial with minimal risk. Placental blood during UCM is directed toward the lungs during a time when there is a rapid fall in pulmonary resistance. Concerns about rapid changes in venous pressure during cord milking were addressed in an early trial that demonstrated no greater increase in venous pressures with UCM compared with uterine contractions or a newborn cry during intact placental circulation. Therefore, UCM should no longer be considered experimental; rather, it is a proven intervention that ensures that premature newborns receive an adequate placental transfusion at birth.

CONCLUSION

UCM provides better hemodynamic and respiratory transition, as demonstrated by trend toward lesser need and a statistically significant reduction in duration of inotrope and respiratory support. Although not statistically significant, lesser incidence of IVH and hemodynamically significant PDA was noted among UCM group, in infants delivered by CD.

UCM should be considered as a beneficial option for preterm infants delivered by CD. Although more larger trials are needed to confirm our observations.

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AUTHORS' CONTRIBUTIONS

VVB conceived the study and contributed to its design, enrolled patients, retrieved, and analyze the data, and wrote the draft of the manuscript. JM retrieved and analyze the data. SK enrolled patients, retrieved, and analyze the data. PK enrolled patients, retrieved, and analyze the data.

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