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Efficacy and Safety of Umbilical Cord Milking Compared to Deferred Cord Clamping in Term Infants: A Randomized Clinical Trial

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ABSTRACT

Deferred cord clamping (DCC) or umbilical cord milking (UCM) are two proposed methods of placental transfusion for term infants; however, it is still controversial as to which method is the best. We aimed to compare the efficacy and safety of DCC and UCM for term infants and their mothers. We conducted a single center, randomized clinical trial (RCT) of mother-infant pairs delivered at King Abdulaziz University Hospital. Infants were randomly allocated to deferring clamping of the cord for 60 seconds or manual stripping of approximately 20cm of the cord over 2-3 seconds that is repeated three times. Seventy-six infants were allocated to UCM group and 73 to DCC group. There were no significant differences between groups with regards to maternal outcomes. There were no differences in the need for resuscitation, apgar scores at one and five minutes and admission to intensive care unit between groups. Of the enrolled infants, 57% (43/76) and 53% (39/73) of the UCM and DCC groups had completed the study respectively. Apart from a significantly higher Hct in infants allocated to DCC both at 24 hours and at 8-12 weeks, there were no significant differences between the two groups in hematological outcomes. Our results showed the efficacy and safety of UCM compared to DCC in term infants. The adoption of UCM may be considered as an alternative care treatment, especially in cases that are not candidates for DCC.

KEY WORDS: CORD CLAMPING, UMBILICAL CORD MILKING, PLACENTAL TRANSFUSION, TERM, INFANT, NEWBORN.

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INTRODUCTION

Active management of the third stage of labor has been shown to reduce the risk of postpartum hemorrhage (PPH),(Prendiville et al., 2000), a leading cause of maternal morbidity and mortality.(Bonnar, 2000, Kumar et al.) Clamping the umbilical cord is part of the management procedures of the third stage of labor. (McCann and Ames, 2007) The optimal timing of cord clamping and its effect on neonatal outcomes is an active research area in the past decade. (Mercer et al., 2018) Placental transfusion passively through deferred cord clamping (DCC) or actively through umbilical cord milking (UCM) allows excess residual cord blood to be transferred to neonate rather than going as waste. Both techniques of handling the umbilical cord at birth have been shown to be feasible, effective and safe.(Katheria et al., 2017) In term infants, both UCM and DCC are associated with increased iron storage and reduced risk for anemia compared to immediate cord clamping (ICC).(Alzaree et al., 2018, Das et al., 2018) There was no reported increased risk of hyperbilirubinemia requiring phototherapy or polycythemia from trials comparing UCM or DCC to ICC.(Chiruvolu et al., 2020) Similarly, there was no reported increased risk of maternal complications including PPH.(Panburana et al., 2020).

Maternal and infant conditions for which active management of placental delivery or resuscitation of the neonate are needed preclude DCC. Umbilical cord milking, which is achieved in seconds rather than minutes, allows active transfer of additional blood to the infant at a rapid rate and within a short time without delaying neonatal resuscitation or the active management of placental delivery. In fact, in suspected or pre-empted neonatal asphyxia it can lead to transfer of important stem cells that may help in regeneration of neurons which is an actively researched area.(Katheria et al., 2019) However, there are concerns of acute non-physiological volume overload with UCM. Despite the available evidence that supports the implementation of UCM, it is not part of the international guidelines of handling the UC at birth. The aim of this study was to compare the efficacy and safety of UCM to DCM in term neonates and their mothers.

MATERIAL AND METHODS

We conducted a single center RCT comparing DCC to UCM in term infants. The study was conducted between March 2015 and December 2016 at King Abdulaziz University Hospital, Jeddah, Saudi Arabia. The study is registered at the International Standard Randomized Controlled Trial Number (ISRCTN) (Trial ID (ISRCTN15174417)). Moreover, the Biomedical Ethics Unit at King Abdulaziz University Hospital approved this research (HA-02-J-008).

Study population: We included pregnant mothers with anticipated full-term birth at gestational age (GA) > 37 weeks. Gestational age was confirmed by first trimester ultrasonography or was based on solid last menstrual period. We excluded monozygotic twin pregnancy, suspected placenta previa, placental abruption, major congenital abnormality, vasa previa, mothers with Rh sensitization, fetal hydrops, women who had unexplained significant vaginal bleeding as assessed by obstetrician 24 hours prior to delivery, ultrasound diagnosis of umbilical cord knot, and women with known human immunodeficiency virus, or hepatitis virus infections.

Research setting and Study design: We conducted an open parallel-arm RCT. The trial was conducted between March 2015 and December 2016 at King Abdulaziz University Hospital, Jeddah, Saudi Arabia. We identified women who fulfilled the inclusion criteria at the time of admission to the labor and delivery ward, along with their partners, and obtained written informed consent from both parents. All participants were free to withdraw from the research at any given point. he mother-infant pair was randomly allocated to either DCC or UCM group. The allocation was performed using a computer-generated list prepared by an independent biostatistician. Random numbers were generated in 1:1 allocation, without stratification, and the record was kept confidential to primary investigators. The allocation codes were placed in sequentially numbered opaque and sealed envelopes. The envelopes were kept in the delivery room in a lock and key cabinet and were the responsibility of the in-charge nurse at delivery room. The head nurse opened the envelope once she verified that the mother was eligible and had consented to participate in the trial. The obstetrician, pediatrician, and involved nurses were knowledgeable of the intervention because they were required to be present at the time of delivery. Staff members who collected blood samples from infants or subsequent data from medical charts and those who performed the analysis were blinded to which group each infant was allocated.

Intervention: Once the laboring woman consented to the study and delivery was impending, the head nurse opened the envelop with the intervention allocation. Before starting the trial, all medical personnel in the labor and delivery unit received training in the study techniques. Neither DCC nor UCM were practiced in the hospital before the study. In the DCC group, the cord was clamped after 60 seconds. The attending nurse measured the time from full expulsion of the fetus from mother to clamping the umbilical cord using a stopwatch that was available in every room. The delivering staff performed UCM by manually stripping an approximately 20 cm of the umbilical cord over a period of 2-3 seconds and repeated the procedure three times before clamping the cord. For both intervention groups, the delivering staffs were instructed to hold the infant at the level of the introitus in vaginal delivery and on the mother's lap when they were born by cesarean section (CS). The obstetric care was otherwise according to the standard practice at the hospital. The following data were collected from maternal charts (age, parity, diabetes, hypertension, and hemoglobin (Hgb) before delivery). The length of third stage, amount of blood loss and whether there was PPH (blood loss more than 500 cc after vaginal delivery and more than 1000 cc after CS delivery in the first 24

hours after delivery) or need for manual removal of the placenta were recorded after delivery.

Infants were cared for according to the hospital routine. Resuscitation of neonates, when needed, was according to Neonatal Resuscitation Protocol (NRP) and was similar in both groups. The neonatal nurse assessed the infant initially and recorded temperature, heart rate, respiratory rate and blood pressure at one hour of age. Infants were examined daily by the physician on service who was not aware of the allocation intervention as per the clinical routine in the hospital. Nurses collected blood for Hgb, hematocrit (Hct) and bilirubin at 24 hours with the metabolic screening. Clotted blood samples were not repeated. Further blood tests needed were done according to clinical evaluation. Infants were then given an appointment at 8-12 weeks for a follow up and to have their blood samples tested for Hgb, Hct and ferritin. The follow-up appointment was given at the time of the scheduled two months vaccination to make it easy for parents to bring their infants. The parents of the enrolled infants were divided into groups according to the date of birth and the scheduled time for follow up to make it easy for the researcher to communicate with a group of parents using a phone assistive communication application. Parents were approached a month, two weeks and three days before the appointment to remind them with the appointment.

Outcomes: The primary outcome of our study was serum ferritin (ng/mL) at 8-12 weeks of age to evaluate infant's iron status. The secondary outcomes comprised of maternal and neonatal outcomes. Maternal outcomes included mortality, estimated blood loss, PPH (blood loss more than 500cc within the first 24 hours following birth), the need for manual removal of retained placenta, and length of third stage of labor. Neonatal outcomes included apgar score at one and five minutes, the need for resuscitation beyond suction and gentle simulation, NICU admission, hematological parameters at 24 hours of life (Hgb [g/dL], Hct [%]), maximum bilirubin level [umol/L], polycythemia (venous Hct > 65%), need for phototherapy and measures of anemia and iron stores at 8-12 weeks of life (Hgb [g/dL] and ferritin [ng/mL]).

Sample size calculation: A total sample size of 120 infants was required to detect a 30% difference in mean ferritin levels between the two enrolled groups, with a sample power of 80% and significance level of 0.05. Assuming that approximately 20% of infants would be lost due to follow-up issues, a total of 150 infants were required

Statistical analysis: SPSS for Windows, version 21.0 (SPSS, Chicago, IL, USA) was used for statistical analysis. Continuous variables were compared using the Student's t test when they were normally distributed and Mann-Whitney U test when skewness in distribution was observed. Chi-square test was used to compare categorical variables between groups. A P value <0.05 was considered significant. Analysis was performed on an intention to treat approach.

Table 1. Demographic characteristics of mother-infants pair

Variable	Delayed cord clamping N=73	Umbilical cord milking N=76	P value
Maternal characteristics			
Maternal age, years, mean (SD)	29.6 (5.6)	29 (6.1)	0.60
Parity, median (IQR)	1 (0,3)	2 (1,3)	0.69
Diabetes, n (%)	7 (9.6)	11(14.5)	0.36
Hypertension, n (%)	1 (1.4)	2 (2.6)	0.58
Cesarean section, n (%)	19 (26.0)	20 (26.3)	0.97
Use of additional uterotonic drugs, n (%)	12 (16.4)	16 (21.1)	0.47
Hemoglobin before delivery, g/dL, mean (SD)	11.4 (1.4)	11.0 (1.4)	0.14
Infant characteristics			
Gestational age, weeks, mean (SD)	39 (1.4)	39 (1.5)	0.75
Birth weight, grams, mean (SD)	3171 (393)	3163 (435)	0.90
Male, n (%)	34 (46.6)	41 (53.9)	0.37

Abbreviations: IQR, interquartile range; SD, standard deviation

RESULTS AND DISCUSSION

One hundred and forty-nine mother-infant pairs were recruited for this study, of which seventy-three were allocated to DCC and seventy-six to UCM. (Figure 1) The demographic characteristics of mother-infant pair are depicted in Table 1. There were no significant differences between the DCC and UCM groups with respect to maternal outcomes. (Table 2) There were no reported maternal deaths in both groups. Studied neonatal outcomes before discharge from hospital did not show significant differences between groups, except for significantly higher Hgb (mean difference, 0.9 g/dL [95% CI, 0.2-1.6 g/dL], p = 0.01) and Hct (mean difference, 2.7% [95% CI, 0.7-4.6%], p < 0.01) at twenty-four hours after birth. (Table 3) Despite repeated reminders, 54.8% (40/73) of infants allocated to DCC and 55% (42/76) of those in the UCM group attended follow up at 8-12 weeks. Reasons for loss to follow-up are shown in Figure 1. While Hct level continued to be significantly higher in the DCC group (MD, 1.8% 95% CI [0.3-3.3%], p = 0.02), Hgb (mean difference, 0.5 g/dL 95% CI [-0.05-1.0 g/dL], p = 0.08) and ferritin (mean difference, 48 ng/ml 95% CI [-19, 116 ng/ml], p = 0.16) were not different between groups among those who were followed. There were no significant differences in baseline characteristics and neonatal and maternal outcomes between those who dropped out and those who completed follow-up. (Table 4).

In this pragmatic, single-center, unmasked RCT of full-term neonates, we identified that there was no difference in maternal, neonatal and infantile outcomes between those who were allocated to DCC for 60 seconds and those whose UC was milked for three times over 2-3 seconds

Table 2. Maternal outcomes

Variable	Delayed cord clamping N=73	Umbilical cord milking N=76	P value
Post-partum hemorrhage, n (%)	1 (1.4)	3 (3.9)	0.33
Manual removal of placenta, n (%)	4 (5.5)	5 (6.6)	0.78
Estimated blood loss, mls, mean (SD)	322 (219)	326 (202)	0.91
third stage of labor Minutes, mean (SD)	4.7 (2.7)	4.7 (4.3)	0.91

Abbreviations: SD, standard deviation

Table 3. Neonatal outcomes in infants who were randomized to deferred cord clamping or umbilical cord milking

Variable	Delayed cord clamping N=73	Umbilical cord milking N=76	Mean difference (95% CI), P value
Outcomes before discharge from hospital			
Need for resuscitation, n (%)	2 (2.7)	2 (2.6%)	0.97
Apgar score at 1m, median (IQR)	9 (9, 9)	9 (9, 9)	0.28
Apgar score at 5m, median (IQR)	10 (10, 10)	10(10, 10)	0.84
Admission temperature, °C, mean (SD)	36.7 (0.19)	36.6 (0.2)	0.03 (-0.4, 0.1), 0.40
Admission systolic blood pressure, mm Hg, mean (SD)	66 (9)	65 (8)	1.4 (-1.5, 4.2), 0.35
Admission diastolic blood pressure, mm Hg, mean (SD)	36 (7.2)	36 (8.5)	-0.2 (-2.8, 2.4), 0.91
Hemoglobin (24h), g/dL, mean (SD)	19.1 (2.2)	18.2 (2.1)	0.9 (0.2, 1.6), 0.01
Hct (24h), %, mean (SD)	53.3(5.9)	50.6 (6.0)	2.7 (0.7, 4.6), 0.01
Bilirubin (24h), umol/L, mean (SD)	95 (33)	91 (34)	4.5 (-6.3, 15.4), 0.41
Maximum bilirubin, umol/L, mean (SD)	115 (55)	110 (58)	5.2 (-13, 23.6), 0.57
Need for phototherapy, n (%)	19 (26.0)	12 (15.8)	0.12
Polycythemia, n (%)	2 (2.7)	0 (0)	0.15
Admission to NICU, n (%)	1 (1.4)	2 (2.6)	0.58
Outcomes at 8-12 weeks			
Hemoglobin, g/dL, mean (SD)	11.5 (1.1) n=37	10.9 (1.2) n=41	0.5 (-0.05, 1.0), 0.08
Hematocrit, %, mean (SD)	33.0 (3.4) n=37	31.3 (3.2) n=41	1.8 (0.3, 3.3), 0.02
Ferritin, ng/mL, mean (SD)	233 (190) n=39	185 (109) n=43	48 (-19, 116), 0.16

Abbreviations: IQR, interquartile range; NICU, neonatal intensive care unit; SD, standard deviation

except for the higher Hct values in the DCC group. In our study, one mother in DCC arm and three mothers in the UCM arm had PPH and the estimated mean blood loss was 322 (±219) and 326 (±202) in DCC and UCM groups, espectively. The mean length of the third stage was similar in both groups and within the normal range. (Magann et al., 2005) Similar finding of no increased risk of maternal complications in the group assigned to UCM was reported in the literature. (Panburana et al., 2020) The incidence of maternal complications is low and thus would require cumulative evidence from several studies to determine safety from maternal aspects. Like other studies, we identified no difference in the need for resuscitation, apgar scores at one and five minutes. admission to NICU and signs of physiologic stability including temperature and systolic and diastolic blood pressure.(Chiruvolu et al., 2020).

Concerns regarding UCM included the fear of active and rapid infusion of large volume of blood to neonates. Though we did not identify any difference in baseline physiological measures between groups, our data should be interpreted with caution as we only included a relatively and potentially healthy group of neonates in our study. This group of neonates as compared to the sicker or more premature group may relatively easily handle an excess of 20-25 ml/kg of volume. Unlike the findings from our study, placental transfusion is reported to increase iron stores at birth and subsequently in early infancy, (Yadav et al., 2015 Das et al 2018). Two key differences may explain these findings. The timing of clamping the UC was deferred for 90 seconds in the DCC group, while milking of the cord was done after clamping the cord at the placental end leaving 25cm of the cord to be milked. (Yadav et al., 2015).

Surprisingly, the Hct level in our study was significantly higher in the DCC group in the first 24 hours of life as well as at 8-12 weeks of age compared to UCM group. The difference in the method used for both interventions could be responsible for the difference in results between studies. The rate and volume of blood transfer in these two methods of placental transfusion have not been studied adequately in the literature. Similar to published trials comparing UCM to DCC in term infants, there was no significant difference between groups in bilirubin level taken in the first 24 hours of life, maximum bilirubin level during stay in hospital, need for phototherapy and incidence of polycythemia. (Chiruvolu et al., 2020).

Table 4. Baseline characteristics and outcomes of participants who completed follow-up and those who were lost to follow-up

Variable	Completed follow-up N=82	Lost to follow-up N=67	P value
Maternal age, years, mean (SD)	30(5.7)	29 (6.0)	0.19
Parity, median (IQR)	1.5 (0,3)	1 (1,3)	0.67
Diabetes, n (%)	9 (11.0)	9 (13.4)	0.65
Hypertension, n (%)	1 (1.2)	2 (3.0)	0.45
Cesarean section, n (%)	18 (22.0)	21 (31.3)	0.19
Gestational age, weeks, mean (SD)	39.2 (1.5)	39 (1.5)	0.40
Birth weight, grams, mean (SD)	3167(399)	3167 (432)	0.99
Post-partum hemorrhage, n (%)	3 (3.7)	1 (1.5)	0.42
Estimated blood loss, mls, mean (SD)	312 (201)	339 (221)	0.44
Need for resuscitation, n (%)	2 (2.4)	2 (3.0)	0.84
Hemoglobin (24h), g/dL, mean (SD)	18.6 (2.3)	18.7 (2.2)	0.72
Hct (24h), %, mean (SD)	51.7 (6.2)	52.2(5.9)	0.60
Bilirubin (24h), umol/L, mean (SD)	91.7 (30.0)	95.5 (37.1)	0.61
Maximum bilirubin, umol/L, mean (SD)	108 (50.4)	118 (63)	0.28
Need for phototherapy, n (%)	15 (18.3)	16 (23.9)	0.40
Polycythemia, n (%)	1 (1.2)	1 (1.5)	0.89
Admission to NICU, n (%)	2 (2.4)	1 (1.5)	0.68

Abbreviations: IQR, interquartile range; SD, standard deviation

We would like to acknowledge the strengths and limitations of this study. The main strength of this study includes masking of outcome ascertainment and clinical care post-placental transfusion. Other crucial aspect of our study was compliance from our obstetric colleagues in attaining a remarkably high success of implementation of allocated intervention. However, loss of follow up was one of the major challenges we faced in this study. Although we had scheduled regular communication with the participants, we had a high rate of attrition. Unfortunately, it is the state of affairs at our institute, which reside in a large metropolitan city encompassing population of differing socioeconomic status.

CONCLUSION

In conclusion, we identified that UCM is effective and safe method of placental transfusion in term infants. However, firm conclusions regarding efficacy could not be made due to significant lost to follow up data for our primary outcome at 8-12 weeks. Umbilical cord milking has the advantage of expeditious handling of the umbilical cord and consequently less resistance of adopting it by the maternal-fetal caregivers in anticipation that resuscitation of the neonate may be needed. However, further research is needed to address the concern about acute and rapid bolus administration in case of UCM rather than gradual equilibration that takes place in DCC. Further, standardization of UCM by specifying the length of the cord to be milked and the rate and the number of times of milking is another area for potential further research.

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Author contribution: H.A. and F.M designed the study. F.M., E.A. and B.E. performed experiment. F.M., E.A. and B.E collected data. H.A, N.B and P.S analyzed data. H.A and F.M wrote the manuscript. N.B and P.S gave technical support and conceptual advice. H.A. critically reviewed the manuscript and supervised the whole study process. All authors read and approved the final manuscript.

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