Effects of umbilical cord milking compared to differed cord clamping in term infants, a randomized controlled trial

Piyadigama I [a], Devasurendra LC [b], Dissanayake AD [c] , Gunawardana K [d]

Abstract

Introduction: Differed cord clamping (DCC) at delivery is currently recommended to increase neonatal haemoglobin levels (Hb) and reduce the risk of infant anemia. It needs waiting for two to three minutes, which is considered to be associated with most of its unwanted effects. An alternative could be umbilical cord milking (UCM) with early clamping. Although effects of UCM have been assessed in preterm neonates such evidence is sparse for term neonates.

Objectives: To evaluate whether the effects on Hb, bilirubin and haemodynamic parameters in infants, and blood loss in the mother are better with UCM than with DCC during elective caesarean delivery at term.

Methods: Sixty term pregnant mothers undergoing elective caesarean delivery (CD) in Teaching Hospital Kandy, from 1st February to 31st March 2015 were randomized to UCM and DCC. The UCM group had the umbilical cord milked towards the umbilicus of the baby in a standard method soon after delivery. The DCC group had the umbilical cord clamped after two minutes of delivery or once the cord pulsations had ceased. Neonatal Hb, bilirubin and haemodynamic parameters, and maternal blood loss were assessed within 48 hours of delivery.

Results: Thirty three participants underwent UCM while 27 participants underwent DCC. Main indications for the CD were past CD (47%), failed induction (12%), past bad obstetric history (10%), maternal medical conditions (8%) and suspected gross cephalo pelvic disproportion (8%). All CD were performed under spinal aneasthesia.

There were no significant differences between the UCM and DCC groups with regard to mean neonatal Hb (17.6g/dl, sd 2.0 vs 17.4g/dl, sd 2.4, p=0.67), mean neonatal total bilirubin (111.8 mmol/l, sd 47.6 vs 123.0mmol/l, sd 35.0, p=0.69) and mean maternal decrease in Hb (1.0g/dl, sd 0.7 vs 1.3g/dl, sd 1.0, p=0.37). All the neonates had birth APGAR of 10 at 5 minutes. The volume of blood remaining in the placenta was significantly higher in the UCM group (29.5ml, sd 20.3 vs 19.5ml, sd 13.1, p=0.03).

Conclusions: Neonatal and maternal outcomes are not better with UCM than with DCC during elective CD.

Key words : Umbilical cord milking, Delayed cord clamping, Term, Haemoglobin, Bilirubin, Blood loss, Caesarean

[a] *Senior registrar in Obstetrics and Gynaecology, University Obstetrics Unit, Colombo South Teaching Hospital, Colombo, Sri Lanka.*

[b] *Medical officer, Colombo South Teaching Hospital, Colombo, Sri Lanka.*

[c] *Senior registrar in Obstetrics and Gynaecology, Sri Jayewardenepura Hospital, Colombo, Sri Lanka.*

[d] *Professor and chair, Department of Obstetrics and Gynaecology, University of Peradeniya, Sri Lanka*

Correspondence: Dr. Indunil Piyadigama MBBS MD

E mail - indu_doc@hotmail.com

https://orcid.org/0000-0002-3929-1330

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INTRODUCTION

Anaemia in children is a common problem in Sri Lanka. According to the National Demographic and Health Survey 2006-7 the prevalence of anaemia among children under five years was 32.6%[1]. The main contributor for childhood anaemia is iron deficiency. Iron deficiency can be detrimental to the development of neonates further progressing to childhood. Improving haemoglobin (Hb) by 1g/dl will lead to a significant reduction in perinatal mortality and mental retardation[2].

The amount of blood in the feto-placental circulation of a term neonate is estimated to be 120ml/kg. At the time of delivery with early cord clamping (ECC) this amount is distributed in a ratio of 2:1 to the fetus and the placenta respectively. Therefore with ECC 78 ml/kg of blood is estimated to be in the newborn circulation. Alternatively with deferred cord clamping (DCC) where clamping of the cord is differed approximately for about three minutes this distribution will be more towards the fetus in a ratio of about 7:1. DCC for three minutes will result in mounting of the blood in the fetal circulation up to 105ml/kg[3, 4].

The value of DCC against ECC had been studied by several randomized control trials (RCT) and meta-analyses over the years. The conclusion drawn from these studies is that there is a significant increase in haematocrit (HCT) as well as Hb in early neonatal life with DCC compared to ECC. Although this beneficial effect was not apparent in Hb by four months of age, the infants with DCC had higher iron stores reflected by higher serum ferritin levels at four months of age[5, 6]. Therefore it was concluded that DCC was a low cost intervention for preventing neonatal and infant anaemia[7].

As DCC needs waiting for additional 2-3 minutes this can delay resuscitation of a newborn. Therefore it would be

contraindicated in a very preterm neonate requiring ventilator support when a delay of even 30-40 seconds would be detrimental[8,9]. Other risks of DCC are transient tachypnea[10], symptomatic polycythaemia[11], increased blood viscosity[12] and hyperbilirubinaemia[13] of the term infant. However no clinically significant adverse effects consequent to these changes have been demonstrated by well-designed studies.

Earlier descriptions of active management of third stage of labour (AMTSL) describes the administration of prophylactic uterotonics, clamping the umbilical cord within 60 seconds following birth of the infant and controlled cord traction[14]. From 2007 the WHO has recommended DCC as an integral component of AMTSL[15] and DCC continue to be strongly recommended during all births including caesarean deliveries (CD)[16]

It is difficult to describe which individual component of AMTSL reduces the risk of PPH and may be the full package contributes[6]. One of the aims of AMTSL is to reduce the length of the third stage because the longer the placenta remains undelivered, the greater is the likelihood of maternal bleeding[17]. Although ECC is associated with a reduction in the length of the third stage of labour, DCC would be appropriate in all deliveries where there is no increased risk of PPH or the requirement of immediate ventilator support for the neonate[16].

The umbilical cord of a full term human neonate averages 50 to 70cm in length and 2cm in diameter[18]. It is estimated to contain on average 108ml of blood. This is about one third of the blood volume in a term infant, which approximates to about 300ml[19]. The umbilical cord is easily accessible to the operator and if this 100ml of blood can be forced in to the fetus this will invariably improve the fetal circulation with minimal delay. The act can mitigate the maternal and fetal effects of 2-3 minutes delay without hampering the fetal circulation.

There are several studies investigating the effect of UCM on preterm infants. These studies have concluded that in preterm infants UCM significantly increase the immediate Hb as well as the iron stores compared to ECC[20, 21]. Also comparable outcomes with regards to the early Hb in the newborn is seen with UCM compared

to DCC[22]. However there are concerns that forcing the blood by milking could traumatize red blood cells, which could lead to excess serum bilirubin (SB) in the fetus.

Unfortunately there are no published studies comparing UCM with DCC in term neonates. The objective of this research is to study whether UCM is better than DCC in improving Hb in term neonates.

METHODS

A parallel group, superiority, randomized control trial with a 1:1 allocation ratio.

According to previous studies neonatal Hb at 24 hours following DCC and UCM were 17.4 g/dl and 18.6 g/dl (sd 1.5) respectively[20]. Therefore to detect an increase of Hb of 1.2g/dl with 80% power at a 5% significant level the minimum sample size was calculated to be 23 per each arm[23]. Anticipating a drop out rate of 20% due to the inability of obtaining blood from the newborns and technical errors the sample size was increased to 30 per each arm.

Random number allocation sequence was developed. Concealment was done by inserting the code into sealed opaque envelops. On the outside envelopes were sequentially numbered. Envelopes were opened only after anaesthesia. The mother, paediatric team carrying out the initial assessment and the laboratory technicians were blinded.

All pregnant mothers assigned for elective CD at term from 1st of February to 31st March 2015 in Teaching Hospital Kandy (THK) were assessed for eligibility for recruitment. Multiple pregnancies, Rh negative mothers, maternal diabetes, oligohydramnios and estimated fetal weight below 2.5kg and above 3.5kg were excluded from the study. Selected mothers were given the consent forms and explained about the study by the principal investigator. Preoperative Hb of the participants were checked by drawing venous blood and the dating was rechecked going through the dating scans.

All the subjects underwent the CD under spinal anaesthesia at the Operating Theatre C of THK. The operating team was briefed on the research and three surgeons who were trained on the two methods of umbilical cord clamping carried out all the surgical procedures. Following delivery of the fetus all

subjects were given intravenous oxytocin 5IU slowly according to the guidance on AMTSL. The DCC group at this point had the umbilical cord clamped after 2 minutes or once the cord pulsations had ceased which ever was earlier. The baby was covered with a sterile, dry and warm cloth to prevent hypothermia, and placed on the mother's thighs, until the cord was clamped and divided, in the DCC group. The UCM group had the umbilical cord milked towards the umbilicus of the baby three times with a 10cm/s speed per stroke followed by clamping of the cord 3 cm from the umbilicus. Rest of the surgery was carried out in the routine manner with two-layer closure of the uterus and meticulous achieving of haemostasis. Peritoneal defects were not sutured.

Routine postoperative monitoring was carried out after the CD. All subjects had an intravenous infusion of 500ml of normal saline over six hours followed by early establishment of oral feeds. All the mothers were discharged within three to four days of delivery and were informed of the blood investigation results of themselves as well as their newborns. They were offered the routine follow up at six weeks at THK.

Primary outcome of the study was the neonatal Hb and HCT within 24 to 48 hour of delivery. Neonatal APGAR and heart rate at 5 minutes, neonatal total serum bilirubin values within 24 to 48 hours after delivery and maternal blood loss were considered the secondary outcomes.

The newborns were immediately taken to the radiant warmer and the attending midwife and the peadiatric house officer assessed APGAR scores and neonatal heart rate at 5 minutes. Venous blood samples were withdrawn from the newborns within 24 to 48 hours of delivery for assessment of venous Hb, HCT and the serum total bilirubin levels. Venous blood samples for maternal postoperative Hb were withdrawn within 24 hours to 48 hours of the procedure and compared with preoperative values for assessment of blood loss. Additionally the volume of blood remaining in the placenta was measured by keeping the placenta on a funnel with a measuring beaker attached to it. Venous Hb and HCT were assessed by the automated analyzer Sysmex, XN 1000 (Japan) and the serum bilirubin levels were assessed by the automated analyzer Beckman Coulter, AU 480

(Japan). Analyzers were quality controlled and calibrated daily.

Results of the two groups were compared using independent sample t test for comparison of means and chi-squared test for comparison of proportions.

RESULTS

Hundred and twenty-eight pregnant mothers undergoing elective CD were assessed for eligibility. Sixty subjects who fulfilled the inclusion criteria and gave consent were recruited for the study. Out of them 27 (45%) subjects underwent DCC while 33 (55%) subjects underwent UCM.

Due to blood collection errors and mothers leaving the trial not giving consent for neonatal blood drawing only 47 samples were available for analysis of the primary outcome. This consisted of 22 (48%) from the DCC group and 24 (52%) from the UCM group. (Figure 1)

There was no significant difference in characteristics of the participants between the two groups (Table 1)

There were no significant differences between the UCM and DCC groups with regard to mean neonatal Haemoglobin (17.6g/dl, sd 2.0 vs 17.4g/dl, sd 2.4, p=0.67), mean neonatal haematocrit (54.5%, sd 7.5 vs 54.9%, sd 8.5,

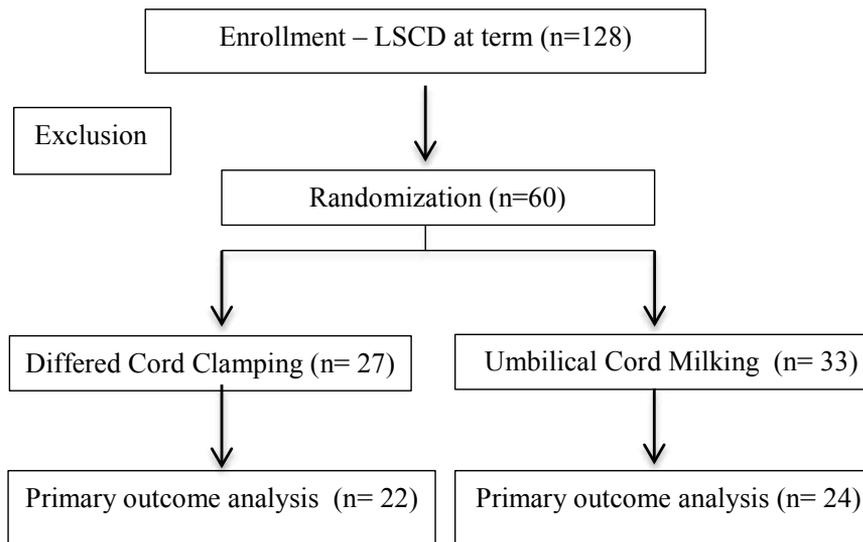## Figure 1 – Flow Chart of the Trial


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Enrollment – LSCD at term (n=128)
                    ↓
Exclusion      Randomization (n=60)
            ↓                      ↓
Differed Cord Clamping (n= 27)   Umbilical Cord Milking (n= 33)
            ↓                      ↓
Primary outcome analysis (n= 22)   Primary outcome analysis (n= 24)
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Table 1 – Characteristics of the participants, their baseline interventions and birth outcomes

Characteristics	Group		
	Cord Milking (n=33)	Differed Cord clamping (n=27)	P value
Maternal age in years: mean (sd)	31.1 (4.6)	29.3 (6.6)	0.21
Maternal pre-pregnancy weight in kg: mean (sd)	51.4 (8.1)	50.5 (7.6)	0.66
Maternal Hb in g/dl: mean (sd)	12.0 (1.1)	12.1 (1.2)	0.84
Use of oxytocin (%)	100	100	-
Antenatal iron supplementation (%)	100	100	-
Antenatal folic acid supplementation (%)	100	100	-
Medical conditions (%)	15.2	11.1	0.72
Birth weight in g: mean (sd)	2989 (295.4)	2869 (233.4)	0.09
Placental weight in g: mean (sd)	589 (101.8)	543 (105.6)	0.10
Male gender neonate (%)	51.5	44.4	0.57

Figure 2 – Distribution of neonatal haemoglobin values 24-48 hours after delivery (n=33 UCM, n=27 DCC)
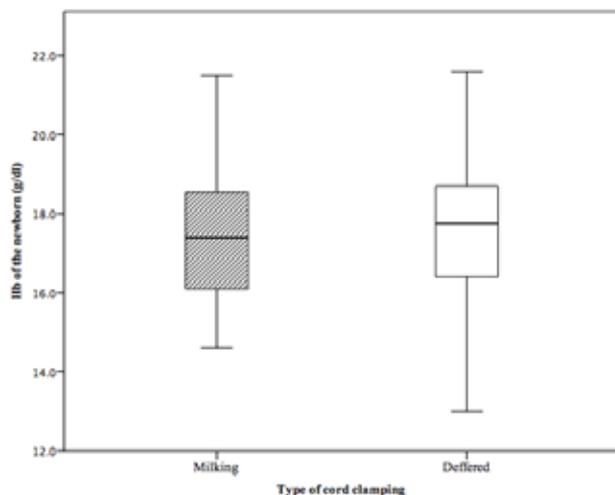

Figure 3 Distribution of neonatal haematocrit values 24-48 hours after delivery (n=33 UCM, n=27 DCC)
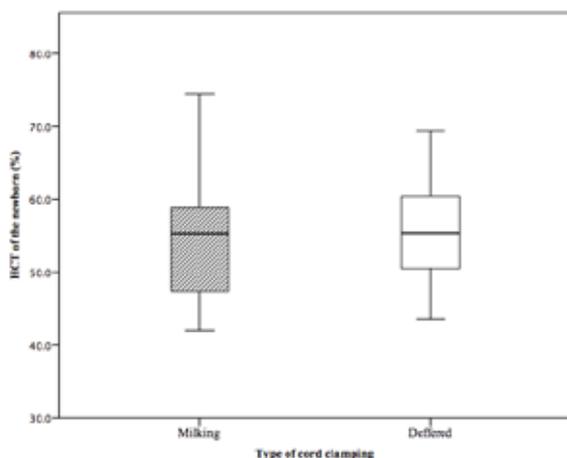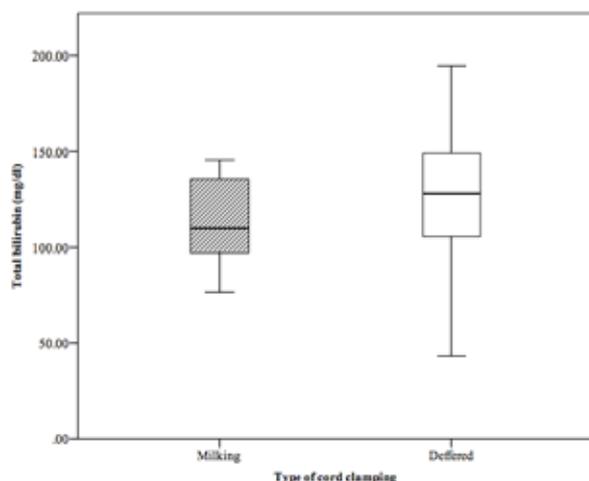

Figure 4 – Distribution of neonatal serum total bilirubin values, 24 - 48 hours after delivery (n=33 UCM, n=27 DCC)

p=0.87), mean neonatal total bilirubin (111.8mmol/l, sd – 47.6 vs 123.0mmol/l, sd - 35.0, p=0.69) and mean maternal decrease in Hb (1.0g/dl, sd 0.7 vs 1.3g/dl, sd 1.0, p=0.37). All the neonates had birth APGAR of 10 at 5 minutes. (Table 2).

However there was a statistically significant increased volume of blood remaining in the placenta in the UCM group (29.5ml, sd 20.3 vs 19.5ml, sd 13.1, p=0.03) and a statistically not significant trend towards a reduction of neonatal heart rate in the UCM group. (128bpm, sd 15.5 vs 119bpm, sd 5.3, p=0.06) (Table 2)

Figures 2-4 show distribution of neonatal Hb, HCT and serum total bilirubin values 24-48 hours after delivery

DISCUSSION

Our results could not show that UCM was better than DCC with regard to increment in neonatal Hb and HCT. Although UCM did not result in any adverse perinatal outcomes as measured by neonatal serum bilirubin levels and APGAR scores, the study was not powered to detect these adverse effects.

There were several studies comparing UCM with DCC in preterm infants. But we could not find similar studies in term infants in the documented literature. Study by Rabe et al was similar to ours except that it was conducted in preterm neonates[22]. The results were comparable to our outcomes with neonatal HB values being 17.5g/dl for UCM and 17.3g/dl DCC group.

The increment in Hb did not reach a statistically significant level. This may be due to our study sample not being large enough to elicit this difference. Also we noted that significantly higher amount of blood was left in the placenta in the UCM group compared to DCC group. If this amount could be forced to the fetus it might have increased the Hb in the newborns of UCM arm further. Previous studies conducted had different number of sweeps (ranging from two to four) used for UCM[9, 22, 24]. Our method consisted of only three sweeps of the cord. Therefore if the number of sweeps were increased to four the effect may be higher reaching statistical significance.

Katheria at el studied haemodynamic changes in preterm infants following immediate cord clamping compared to UCM[25]. Although No difference was

Table 2 – Outcomes

Outcome	Group		
	Cord milking (n=33)	Differed cord clamping (n=27)	p Value
Hb of the newborn in g/dl: mean (95% CI)	17.6 (16.8-18.5)	17.4 (16.3-18.5)	0.67
HCT of the newborn (%): mean (95% CI)	54.5 (51.2-57.8)	54.9 (50.9-58.9)	0.87
APGAR of 10 at 5 minutes (%)	100	100	-
Neonatal heart rate at 5 minutes of birth in beats per minute: mean (95% CI)	119 (117-123)	128 (118-140)	0.06
Total bilirubin of the newborn in mmol/l: mean (95% CI)	111.8 (88.9-134.7)	123.0 (106.7-139.4)	0.67
Maternal Hb decrease in g/dl: mean (95% CI)	1.0 (0.7-1.4)	1.3 (0.9-1.7)	0.37
Blood left in placenta in ml: mean (95% CI)	29.5 (22.0-36.9)	19.5 (14.2-24.7)	0.03

found in heart rate and blood pressure they found an increase in superior vena cava blood flows and systemic blood flows. 10% (119 bpm in UCM vs 128 bpm in DCC) this is probably of no clinical significance. However if the number of sweeps were increased to further increase Hb levels in neonate, this may lead to a further drop in FHR making the effect clinically significant.

Cochrane review by McDonald at el showed that there is no significant difference in the risk of moderate to severe post partum haemorrhage by the timing of cord clamping (RR - 1.04, 95%CI 0.65-1.65)[6]. In our study the haemoglobin drop was 1.3g/dl for the DCC group and 1.0g/dl for the UCM group. The Hb drops in our study were higher in comparison to the meta-analysis findings. This difference may be explained by the fact that the entire subject underwent CD with a higher blood loss compared to most undergoing vaginal deliveries in the Cochrane review.

STRENGTHS AND LIMITATIONS

The main strength of our study was the meticulous way of cord milking, which was standardized and was carried out only by three surgeons who were trained on the exact method.

Primary end point of the study was neonatal Hb. There were difficulties associated with blood collection, which led to dropouts from the study. The difficulties encountered were the mothers changing their minds and not giving consent for blood collection of their newborns following CD, collection errors such as unable to get an adequate sample as well as clotting of the samples during transport. Since we further inflated our sample by 20% expecting these dropouts we were able to overcome this problem without compromising on the quality of the research. However the sample size was calculated to assess the primary end point. Therefore the study was not powered enough to assess for adverse perinatal outcomes.

We did not measure the circulating blood volumes in neonates. Blood volume assessment can be done with either biotin labeling or red cells method, which is time consuming, expensive and difficult to perform on a large number of neonates or diluting adult hemoglobin in fetal blood and comparing this with circulating fetal hemoglobin, which is limited to neonates who require a donor blood transfusion[23, 25]. Due to these limitations we adhered to measurements in venous Hb and HCT .

CONCLUSIONS AND RECOMMENDATIONS

UCM was not better than DCC in increasing neonatal Hb within 24 hours of birth following elective CD. However there is no additional risk of neonatal jaundice, worsening fetal haemodynamic parameter or APGAR scores with UCM.

Since the UCM group had significantly higher amount of blood left in the placenta increasing the number of sweeps during milking could further increase the Hb levels in neonates which needs further studies. A trend towards a decrease of FHR in UCM group needs to be further evaluated with an adequately powered sample to detect these subtle adverse perinatal outcomes.

DETAILS OF ETHICS APPROVAL

Ethical approval for the study was taken from the Ethical Review committee of THK.

AUTHOR CONTRIBUTIONS

PI, DAD, GK designed the study. PI and DLC contributed to the data collection. PI and DLC performed the data analysis. PI and DAD prepared the article for submission. PI, DAD and GK revised it critically for important intellectual content. All authors approved the final version.

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