Abstract

Objective of the study was to compare the effect of umbilical cord milking (UCM) and delayed cord clamping (DCC) on hematological parameters (serum ferritin & hemoglobin) at 6 weeks of life in term neonates. It was a Randomized Controlled Trail conducted at a teaching hospital in North India from August 2012 to August 2013. Babies born at > 36 weeks of gestation were randomized in two groups, UCM and DCC (100 in each group). Umbilical cord milking was done after cutting and clamping the cord at 25 cm from the umbilicus. In DCC group, clamping was delayed by 60 to 90 seconds before cutting the cord. The baseline characteristics were comparable in the two groups. Mean serum ferritin (134.0 [89.8]) ng/ml and mean hemoglobin (11.0 [2.4]) gm/dl in umbilical cord milking group was comparable to mean serum ferritin (142.7 [87.0]) ng/ml and hemoglobin (11.3 [2.6]) gm/dl in DCC group at 6 weeks of age. There was no difference in hemodynamic status, cranial Doppler indices and adverse neonatal outcomes among the two groups.

Conclusion: The delayed cord clamping and umbilical cord milking had comparable effect on hematological status at 6 weeks of life, in term neonates.

Key words: Serum Ferritin, Umbilical Cord Handling.

Abbreviations: AAP: American Academy of Pediatrics; AGA: Appropriate for Gestational Age; CI: Confidence Interval; CTRI: Clinical Trial of India; DCC: Delayed Cord Clamping; IDA: Iron Deficiency Anaemia; IUGR: Intrauterine Growth Retardation; NIBP: Non Invasive Blood Pressure; LMP: Last Menstrual Period; NICU: Neonatal Intensive Care Unit; RBC: Red Blood Cell; SGA: Small for Gestational Age; SD: Standard Deviation; UCM: Umbilical Cord Milking.

Introduction

Perinatal iron deficiency has received little attention in the past, due to assumption that infants are protected from iron deficiency unless the mother is markedly anemic. In a survey in India, 70% of infants between 6 and 11 months of age were found anaemic [1]. Iron stores at birth are a major factor influencing growth and the occurrence of iron deficiency anemia (IDA) during infancy [2]. IDA in infancy is of particular concern because of potentially detrimental effects on physical and cognitive development [3]. Iron stores at birth can be affected by trans-placental transfer of iron and blood from the placenta and cord at the time of delivery [1]. To enhance their transfer from placenta and umbilical cord to baby, interventions like umbilical cord milking and delayed cord clamping have received a lot of scientific attention. They serve to potentially enhance neonatal blood volume and consequently iron stores after birth.

Delayed cord clamping (DCC) in which clamping of cord is delayed by 30 to 180 sec has been shown to improve the hematological status in both preterm and term infants [4-9]. However, a recent meta-analysis [10] reported that delayed cord clamping is only marginally beneficial in reducing anemia in term neonates. There is also concern of hypothermia and delay...
Materials and Methods

This randomized controlled trial (parallel group study with 1:1 randomization) was conducted in the Department of Paediatrics, Neonatal Unit and Department of Obstetrics, LLRM Medical College, Meerut, India between, August 2012 to August 2013. The study was approved by the Institutional Ethical Committee (IEC), LLRM Medical College, Meerut, India. It was also registered with Clinical Trial of India (CTRI) no. [CTRI/2013/01/003323]. Informed, written consent taken from parents before delivery from the eligible mothers in local language (Hindi). The inclusion criteria for the trial were term newborn babies born at >36 weeks of gestation as effective as delayed cord clamping in improving hematological status at birth and at 6 weeks of life with comparable hemodynamic effects after birth.

The exclusion criteria was, umbilical cord length < 25 cm or cord anomalies like true knots or cord prolapse, multiple births (twins, triplets), babies of Rh negative and retro virus positive mothers, antenatally diagnosed major congenital anomalies or apparent at birth, babies those were limp at birth, hydrops fetalis and meconium stained non-vigorous babies. The primary outcome of the study was hemoglobin (Hb) and serum ferritin in early infancy, without causing any significant side effects.

Randomization, allocation concealment and blinding

Randomization was done just after delivery after ensuring the adequate length of umbilical cord. All babies fulfilling inclusion criteria were divided into two groups of 100 each.

i. Umbilical cord milking after immediate clamping (UCM group).

ii. Delayed cord clamping of cord performed at 60-90 sec after delivery of baby (DCC group).

Babies in both groups received routine care at birth as per unit protocol [15].

Intervention

The interventions (UCM or DCC) which are written on the slip were carried out by the pretrained doctor on duty. Laboratory investigator and person providing care along with recording hemodynamic parameters in NICU in first 48 hours were blinded to the intervention. Blinding of the clinicians was not possible as the neonatal team was present in the delivery room as well as because of nature of the interventions.

In all cases after birth in either group, the babies were held at the level of the introitus in vaginal delivery and over the thighs of mother in caesarean section while the umbilical cord was cut and clamped. In UCM group the cord was cut and clamped as soon as possible to avoid placental transfusion before clamping and cases excluded if the time exceeds 30 seconds. The cord was cut at approximately 25 cm of length from umbilical stump, and then the baby was placed under the radiant warmer. The length of umbilical cord length (25 cm) was measured using sponge holding forceps (26 cm) used for clamping. Three resident doctors involved in delivery and newborn resuscitation were trained for technique of cord milking by showing 3 live demonstrations by primary investigator and a video available on the Internet [16]. The umbilical cord was raised and milked from the cut end toward the infant 3 times with speed at 10 cm/sec, and then clamped 2-3 cm from the umbilical stump. The delivering obstetrician was informed about the intervention to delay the clamping for 60-90 sec which was noted by using the wall-mounted clock in delivery room. According to obstetric protocol, oxytocin was given just after delivery of the fetus to all deliveries.
After delivery, the babies were kept with mothers unless they required admission in NICU for standard indications. Early breast feeding was encouraged in all babies as per standard guidelines. The infants were evaluated at birth, 24 hrs and then at 48 hrs for adequacy of feeding, any signs of respiratory distress or sepsis. Heart rate, respiratory rate and blood pressure were recorded at 30 mins, 24 hrs, and 48 hrs. Blood pressure was recorded by oscillating NIBP (Schiller) in right arm using a size “0” cuff for term babies with bladder dimension of 6 cm. Heart rate, respiratory rate were checked by auscultation of precordium & inspection of chest respectively. Blood samples were collected in EDTA tubes (BD Vacutainer) for hemoglobin and PCV at 30 min and at 48 hrs of life and in serum separator tubes (BD Vacutainer) for bilirubin at 48 hrs and serum ferritin at 6 weeks of life. Hemoglobin was measured by SAHLI’S hemo-globinometer, serum bilirubin by Jendrassik & Grof method, Packed Cell Volume by MICROHAEMATOCRIT METHOD and serum ferritin by ELFA (one step enzyme immunoassay sandwich method with a final fluorescent detection) using kit made by BIOMERIEUX Company. Cranial Doppler indices measurement was performed at 24 to 48 hrs of life in the middle cerebral artery by placing the 2-6 MHz convex transducer over the temporal bone by using HITACHI ALOKA prosound α6 ultrasound Doppler machine; model no UST-9123, Tokyo, Japan at a low frequency of 3-4 MHz by two investigators.

The phone numbers of enrolled babies’ attendants were recorded and contacted weekly to gain their confidence and were reminded about the follow up at 6 weeks of age, each time. At 6 weeks of age, when infants were scheduled for a DPT vaccination, the follow-up visit was planned for anthropometry measurement (length & weight) along with blood sampling for (hemoglobin & ferritin). The parents were enquired about the mode of feeding.

Sample size and statistical analysis

The sample size was calculated on the basis of a previous trial done in our institute which showed mean hemoglobin level with SD in the intervention arm of term neonates as 11.9 (1.6) g/dl & in the control arm as 10.9 (1.0) g/dl respectively [13]. We used the PS Power and Sample Size Calculations, Version 3.0.43, January 2009 for sample size calculation. For a 2 tailed α value of 0.05 & power of 90%, 85 babies were required in each group to detect a difference in hemoglobin of 1gm/dl with SD of ± 2in neonates in the two groups. Considering the 15% attrition rate on the follow up, the total sample size was upscaled to 100 babies in each group to a trial of 200. Statistical Analysis was done using STATA 11 software. Analysis of continuous data was done by unpaired t test and categorical data was compared using chi square or Fischer exact test as applicable. P value of less than 0.05 was considered significant.

Results

Total 800 newborns were assessed for eligibility. Out of them 600 babies were excluded for different reasons (Figure 1). Out of the 200 newborns enrolled, 185 completed the trial (92 in UCM group and 93 in DCC group). Primary outcomes were analyzed for 185 babies, while all 200 babies were analyzed for secondary outcomes. Figure 1 gives the flow of the study and details of inclusion, exclusion and reason for non-compliance during the course of trial. The baseline neonatal and maternal characteristics like maternal weight, maternal anemia, and mode of delivery, SFD, sex and weight of bay were comparable in the 2 groups (Table 1). Maternal weight and hemoglobin was measured at time of admission before delivery. We had not calculated the body mass index (BMI) of mothers.

The mean (SD) of serum ferritin at 6 weeks in the UCM group was 133.98 (89.82) ng/ml and in the DCC group was 142.66 (87.06) ng/ml (Table 2, Figure 2). The mean hemoglobin at 6 weeks was also comparable in the 2 groups. Analysis of the hematological parameters like hemoglobin, packed cell volume and bilirubin achieved in the first 48 hrs was also comparable in the 2 groups. No significant difference was observed in blood pressure, heart rate and cranial Doppler indices in the two groups. Development of jaundice and need for admission was similar in the two groups (Table 3). None of the infants developed respiratory distress.
median = 11.216
-16.36 to 0
1
1
0.43 (43%)
p Value
0
-0.63 to 1.06
0
0.49
10.65 to 134.0 (89.8)
6.0 (3.0)
0.20
40 (40%)
142.7 (87.0)
0.61
0.77
-2.70 to 0
Figure 2: Box & Whisker plot of serum ferritin level (ng/ml) at 6 weeks.

Table 2: Hematological outcomes.

| Parameters           | Umbilical Cord Milking (n=93) | Delayed Cord Clamping (n=92) | 95% CI of Difference | p Value |
|----------------------|-------------------------------|------------------------------|----------------------|---------|
| Ferritin (ng/ml)     | 134.0 (89.8)                  | 142.7 (87.0)                 | -16.36 to 33.73      | 0.49    |
| Hemoglobin (gm/dl)   | -                              | -                            | -                    | -       |
| 30 min               | 16.9 (2.2)                    | 16.7 (2.3)                   | -0.89 to 0.34        | 0.37    |
| 48 hr                | 11.0 (2.4)                    | 11.3 (2.6)                   | -0.90 to 0.37        | 0.41    |
| PCV (%)              | 51.9 (6.40)                   | 50.3 (6.8)                   | -2.52 to 1.15        | 0.46    |
| 48 hr                | 48.5 (6.8)                    | 48.0 (6.8)                   | -2.38 to 1.39        | 0.60    |
| Serum bilirubin 48 hr (mg/dl) | 5.8 (3.1) | 6.0 (3.0) | -0.63 to 1.06 | 0.61 |

Mean (SD); CI: Confidence Interval; PCV: Packed Cell Volume.

Table 3: Hemodynamics and related neonatal outcomes (up to 48 hrs).

| Parameters               | Umbilical Cord Milking (n=100) | Delayed Cord Clamping (n=100) | 95% CI of difference | p Value |
|--------------------------|--------------------------------|------------------------------|----------------------|---------|
| MBP (mmHg)               | 64.4 (10.9)                    | 62.4 (11.8)                  | -5.16 to 1.18        | 0.22    |
| 30 min                   | 61.8 (10.7)                    | 59.3 (10.9)                  | -5.56 to 0.48        | 0.10    |
| 24 hr                    | 60.1 (10.8)                    | 57.8 (10.1)                  | -5.56 to 0.68        | 0.13    |
| HR (per min)             | 143.3 (8.0)                    | 144.4 (9.0)                  | -1.28 to 3.46        | 0.37    |
| 30 min                   | 132.7 (6.6)                    | 133.3 (7.8)                  | -1.38 to 2.64        | 0.54    |
| 24 hr                    | 127.4 (7.7)                    | 126.2 (7.7)                  | -3.41 to 0.87        | 0.24    |
| RR (per min)             | 47.6 (11.0)                    | 47.2 (3.9)                   | -2.69 to 1.99        | 0.73    |
| 30 min                   | 38.5 (10.5)                    | 37.9 (3.4)                   | -2.75 to 1.59        | 0.60    |
| 24 hr                    | 33.7 (10.7)                    | 32.4 (3.8)                   | -3.62 to 0.86        | 0.23    |
| Temperature (°F)         | 96.9 (0.9)                     | 97.0 (0.9)                   | -0.20 to 0.30        | 0.70    |
| 30 min                   | 98.1 (0.4)                     | 98.0 (0.4)                   | -0.18 to 0.06        | 0.31    |
| 24 hr                    | 98.3 (0.3)                     | 98.3 (0.3)                   | -0.16 to 0.00        | 0.05    |
| Craniol Doppler Indices | 0.65 (0.07)                    | 0.65 (0.08)                  | -0.02 to 0.02        | 0.95    |
| Resistive Index (RI)     | 1.18 (0.26)                    | 1.18 (0.24)                  | -0.07 to 0.06        | 0.91    |
| Pulsatility Index (PI)   | Any Jaundice       | 40 (40%)                      | -10.65 to 16.65      | 0.77    |
| NICU admission for phototherapy | 6 (6%)          | 11 (11%)                     | -2.70 to 12.70       | 0.20    |
| Respiratory distress     | 0                             | 0                            | 1                    |
| Need of oxygen           | 0                             | 0                            | 1                    |
| Jitteriness              | 0                             | 0                            | 1                    |
| NICU admission other than phototherapy | 0 | 0 | 1 |

Mean (SD); CI: Confidence Interval Mean (SD); MBP: Mean Blood Pressure; HR: Heart Rate; RR: Respiratory Rate.

Discussion

This study was performed among Indian patients whose offspring have a baseline increased risk for developing neonatal and childhood anemia. We demonstrated that in full term neonates, the hematological and hemodynamic effects of umbilical cord milking (UCM) with early cord clamping were similar to those of delayed cord clamping (DCC) after 60-90 seconds of birth. Both interventions led to comparable hemoglobin and serum ferritin levels at 6 weeks of age without any significant side effects in initial 48 hours of life.

There have been many trials demonstrating the benefits of DCC on the hematological status in term babies but there have been limited trials looking at the benefits of UCM in general and especially in term neonates. As early as in 1960, Lanzkowsky reported for the first time that DCC has beneficial effects on hemoglobin level of the neonate when he serially assessed them till 96 hours of life [17]. Grajeda et al. [18] also demonstrated that umbilical cord clamping after cessation of cord pulsations resulted in increase in hemoglobin at 2 months of age [18]. An Indian study also demonstrated that mean hemoglobin & ferritin at 3 months of age was significantly higher in DCC group [1]. The largest trial to evaluate the effect of DCC was done on 476 term babies by Chaparro et al. [19] in Mexico. They did serial evaluation of hematological parameters from birth till 6 months of age and reported higher mean corpuscular volume, ferritin, body iron and stored iron [19]. No study has evaluated whether the advantage in hematological parameters persist beyond 6 months of age.

The Cochrane meta-analysis of 11 trials on the effect of delayed cord clamping in term neonates: A Randomized Controlled Trial. Acad J Pediatr Neonatol. 2015;1(1): 555551.
timing of umbilical cord clamping in term infants analyzed both maternal and fetal outcomes. Reviewers found no significant effect on postpartum hemorrhage. The infants who were subjected to DCC had significantly higher hemoglobin by 2.17 gm/dl (95% CI, 0.28-4.06) and higher ferritin by 11.8 ng/ml (95% CI, 4.07-19.53) till 6 months of age [20]. The result of an earlier meta-analysis [21] was also similar to the Cochrane meta-analysis. The above findings are comparable to the results of our study though we evaluated our babies at an earlier age of one and a half months. The high and comparable levels of hemoglobin and ferritin in the newborns of both the groups in our study is probably due to increased blood transfusion from the placenta and cord to the neonate at birth whose benefits extend in to early infancy. In view of various studies demonstrating the benefits of DCC, the American Academy of Pediatrics (AAP) has recently recommended that cord clamping should be delayed by at least 1 minute in uncomplicated deliveries of both term and preterm neonates’ not requiring resuscitation [4].

Although, American Academy of Pediatrics has recommended delayed cord clamping for all newborns, but it may not be feasible in all deliveries, especially in babies who require resuscitation at birth. UCM also increases the placental and cord blood transfusion to the newborn and can potentially improve their hematological status. Hosono et al. [11] conducted the first randomized controlled trial on 40 very preterm infants of 26-29 weeks of gestation and compared UCM to early cord clamping. They demonstrated higher hemoglobin, decreased number of RBC transfusions and shorter duration of ventilation or supplemental oxygen in the milked group [11]. A larger randomized controlled trial on 200 term babies by Upadhyay et al also reported that UCM after birth leads to higher hemoglobin and better iron status at 6 weeks of age as compared to babies receiving early cord clamping [13]. Rabe et al. [14] reported a higher hemoglobin levels than reported by Upadhyay et al. [13], which was possibly related to the milking technique. Rabe et al. [14] milked, when the cord was still attached to the placenta while Upadhyay et al milked after cutting the cord. So in Rabe et al study the baby got more blood due to subsequent refilling of cord from placenta. In this study we used the same technique of our previous trial that was being practiced in our institution.

In UCM group we cut end clamped the cord as soon as possible to minimize the placental transfusion before clamping and excluded the baby if this time exceeds 30 seconds. However even this short period of time the baby might receive some blood before cutting and clamping. We have no data for the mean time taken to cut and clamp the cord in UCM group. Most studies including those mentioned above have compared either UCM [13] or DCC [20, 21] to early cord clamping in term neonates. However, there are only limited trials directly comparing the effects of DCC and UCM in term neonates. Rabe et al conducted the only trial comparing UCM and DCC in preterm infants [14]. They had randomized relatively small number of 58 preterm infants less than 33 weeks of gestation and reported that both procedures are equally efficacious in improving hemoglobin soon after birth and at 6 weeks of life. Though we also found similar results in term babies, the methodology of the above mentioned trial and ours differed in terms of time of clamping, frequency of cord milking as well as position of the baby after delivery. The time to delay cord clamping by Rabe et al was 30 seconds after birth in delayed cord clamping group. We followed the methodology of umbilical cord milking and positioning of baby being held after delivery as in our published earlier by our group [13]. Theoretically, delaying the cord clamping for a longer period of time should lead to more passage of transcord blood than milking due to connectivity to bigger pool of blood in placenta. However, this has not been observed and hemoglobin level in both the groups was found to be comparable in the two studies.

In the present study, the mean hemoglobin and hematocrit level during the initial 48 hrs of life in both the groups were comparable to results observed in previous studies [20,21]. In the Mexican study, the above parameters were found to be significantly higher at 7 hours in the delayed clamping group [19]. In another randomized controlled trial from Argentina, newborns were randomly assigned to cord clamping within the first 15 seconds, at 1 minute, and at 3 minutes after birth. The prevalence of anemia, as defined by hematocrit levels less than <45% at 6 hours, was significantly lower in later two groups than in first group but mean hematocrit level remained within physiologic limits in all the three groups [22]. However, two studies from the Indian subcontinent reported comparatively lower level of hemoglobin during the initial 48 hours of life in both control and intervention arm when compared to studies conducted in developed countries. This could be due to poor maternal health and higher prevalence of maternal iron deficiency in developing countries [13,23].

We found comparable blood pressure in both milking & delayed clamping groups and within normal range of gestational age specific normograms. Two prior studies had reported higher mean blood pressure by about 4-6 mmHg but not above normal range, with UCM [12,13]. This is probably due to transfusion of extra blood into neonatal circulation which could lead to increase in both blood pressure and cardiac output. Though this extra push of blood at birth pumps up the hemoglobin and iron status, there are some concerns about adverse effects of flushing the extra blood into the pressure passive cerebral circulation of neonates. Our study monitored cerebral blood flow in the two groups and found no difference in cranial Doppler indices. They were within reference range for term neonates [24,25] and suggesting that healthy neonates can auto regulate their cerebral blood flow and thus can avoid transmitting fluctuation in the systemic blood pressure [26].

The proportion of babies requiring phototherapy in either group of our study was not only similar, but also not different from need for phototherapy in other reports [27,28]. The present study did not find any baby with symptomatic polycythemia, respiratory distress or need for admission in NICU for reason other than jaundice. Other trials [22,13] and metaanalysis [20,21] also have not reported any increase in above mentioned side effects with the two methods due to increase in transcord blood flow into the baby.
Among intrauterine growth retarded babies there is special concern of polycythemia. In our study, the sub group analysis of babies with intra uterine growth retardation revealed higher mean hemoglobin level at 48 hours of life but without any baby developing polycythemia. Rheezen et al. [29] had also demonstrated higher hemoglobin with DCC in both appropriate for gestational age (AGA) and small for date (SFD) infants at 2-3 months of age. The paucity of data on the effect of DCC or UCM in SFD infant’s warrants further research in this population, as SFD constitutes almost 25% of all of babies in developing countries like India.

The main strength of our study was that it was a randomized controlled trial with appropriate sample size. Our study has few limitations also. Our study had a short duration of follow up. A longer follow up till 6 to 12 months of age is desirable to establish whether the initial advantage in hemoglobin & ferritin sustains later in infancy and early childhood. Another limitation of our study was related to milking technique, we cut the cord and then milked; that limits the refilling of cord from placenta. Other limitations included lack of blinding, limited generalizability and the lack of power for rare adverse outcomes.

Conclusion

For the first time in term babies, our study demonstrated that both UCM and DCC have comparable benefits in improving hematological status at 6 weeks without affecting the cerebral blood flow indices or producing any noteworthy significant adverse neonatal outcomes in initial 48 hours of life. As DCC has already been formulated as standard of care in all deliveries by American Academy of Pediatrics, UCM can be recommended in all deliveries in which DCC is not feasible or not practiced for any reason.

What is already known?

Delayed cord blood clamping improves certain hemotologic parameters for neonates, which is potentially important in populations with high rates of neonatal and childhood anemia, but that delayed cord blood clamping may not be feasible in clinical situations when neonatal resuscitation is urgent.

What this study adds

There is not a significant difference in ferritin and hemoglobin levels at 6 weeks among term, Indian neonates who had UCM and DCC and that this study may give support to the practice of UCM in term deliveries when DCC is not feasible.

Implication for practice

UCM can be used in term neonates as a routine or in conditions where DCC is not feasible. In cases when the neonate requires resuscitation then UCM can be done by the neonatal team attending the baby at delivery. Implication for research: Further studies with longer follow-up are needed to establish the sustainability of the advantage in hemoglobin and serum ferritin later in infancy. Other parameters like cerebral oxygenation and cerebral blood volume could also have been further evaluated. Also, superior venacaval flow indices & ECHO can be studied to seen the impact of extra volume transfused on the cardiac function of the baby.

Financial support

The study was partially funded by 'thesis/ research grant' of Indian Council for Medical Research (ICMR).

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