Original Article

Early versus Delayed Umbilical Cord Clamping Leads to Neonatal Anemia

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Abstract

Objective: To evaluate whether Early Cord Clamping (ECC) leads to anemia and Delayed Cord Clamping (DCC) could improve the haematological status of infants.

Patients and Methods: Interventional randomized trial study was carried out over a period of six months from 1st October, 2010 to 31st March 2011 in Gynecology Department Lady Willingdon Hospital, Lahore. A detailed questionnaire was prepared. Total 300 cases were randomly allocated after taking informed consent. Venous hematocrit values, Bilirubin levels and ferritin were detected after 24 hours, 48 hours and 3 months of neonatal life and the record entered into proforma.

Results: Neonatal anemia and decreased hematocrit level was found in 32 / 150 (21%) neonates with greatest significance due to early cord clamping neonatal. While Delayed cord clamping (DCC) resulted with a higher mean hematocrit (45.6 ± 5.6 versus 32.8 ± 7.1 at the end of three months) and hemoglobin concentration (17.4 ± 2.2 g/dL vs 12.5 ± 4.1 g/dL at the end of 3 months), whilst a non-significant difference was observed in mean bilirubin level in DCC group as compared to ECC group (7 ± 2.3 vs 5 ± 3.5 mg/dL in 48 hours). A significant number of infants developed jaundice in DCC group as compared to ECC groups (8% vs 2%; p = 0.016). No infants polycythemia, mother postpartum hemoorhage was seen in both groups. All the jaundice patients recovered with Phototherapy.

Conclusion: To get the normal hematocrit level in term infants, it is very necessary to avoid early cord clamping and this practice should be changed in modern obstetrical practice as it is not the standard method and the cause of iron deficiency anemia. Delayed cord clamping method increases mean neonatal hematocrit, hemoglobins within a physiologic range and save from developing iron deficiency anaemia although delaying clamping increases the risk of jaundice requiring phototherapy.

Key words: Early Clamping, Hematocrit, Neonatal anemia, Umbilical Cord.

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Introduction

The neonatal umbilical cord clamping and cutting is a natural historical intervention in humans but the optimal timing of this procedure has been a controversial issue for decades.[1]

"Earlier physiological studies have shown that, of the total blood volume in the combined fetal – placental circulation at full gestation, approximately 25% to 60% (54 – 160 mL) is found in the placental circulation and that as many as 60% of the fetal red blood cells are found therein while this blood is also known to be rich in hematopoietic stem cells".[2-4] Iron deficiency anemia is a major worldwide public health problem in the children that affects the physical and mental health of the neonates.[5,6] It has been documented that during the initially the infants largely depend on their mothers for their iron supply for growth and production of hemoglobin.[7] "It has been studied that early cord clamping (ECC) puts the newborn at increased risk of hypovolumic damage and iron loss, as well as of several blood disorders and type 2 diabetes, as a consequence of loss of hematopoietic stem cells."[8] ECC has been reported as a major cause of neonatal anemia and this has led some investigators to recommend delayed cord clamping to prevent this problem without casting any intervention therapy.[6,9,10]

Delayed cord clamping (DCC) has been postulated as a measure to prevent infant iron deficiency as compared to early clamping. A major error in modern obstetrical practice is routine premature clamping of the umbilical. Thousands of Obstetricians have been taught that immediate cord clamping of an acceptable, standard obstetrical procedure and millions of newborn have been subjected to cerebral palsy (CP), along with other injuries can result from premature cord clamping the child's only functioning source of oxygen – the placenta is carrying 30 percent to 50 percent or more of its maternal blood values. Total asphyxia is imposed until the legs function and the depressed (asphyxiated, hypovolumic) child starts, its extra uterine life in hypovolumic shock.[11-13]

Immediate ventilation may not reverse the asphyxia, if there is not enough blood vessels adequately thus the immediately clamped neonate is very prone to hypoxia and ischemia-and to hypoxic – ischemic encephalopathy (HIE). Early cord clamping reduce the extent of placental transfusion to the baby and results in significantly lower haematocrit and hemoglobin levels in newborn.[14] It has been seen that delayed clamping of the cord improves iron status and reduces the prevalence of iron deficiency in new born and reduces prevalence of neonatal anemia, without noticeable adverse effects.[15]

The study was conducted to determine the frequency of anemia in early cord clamping of term infants.

Material and Methods

An interventional randomized trial study was carried out for comparing early and cord delayed clamping in Gynecology Department, Lady Willingdon Hospital Lahore for six months (1st October 2010 to 31st March 2011). A total 300 cases were randomly allocated after taking informed consent in to two groups (2 parallel study groups A and B with equal number of populations as 1:1 randomization). It was a partially blinded randomized controlled trial. Pediatricians and laboratory staff was kept blind. Although study staff did not inform mothers of their assignments, the nature of intervention made it impossible to blind them. LAB (allocation was concealed from LAB staff) for presence or absence of anemia (i.e. haematocrit value) and entered into the proforma. The study was approved by the ethical review committee of King Edward Medical University.

Inclusion Criteria

1. Healthy mother, Non-anemic.
2. Non-smokers and non-diabetics.
3. Mothers not taking anticonvulsants, anti-depressants, thyroid hormone, insulin, chemotherapy, or cortisone.
4. Normal pregnancy with Single baby.
5. Full term pregnancy with 37 to 41 weeks of gestation.
6. With expected normal vaginal delivery and cephalic presentation.

Exclusion Criteria

1. low APGAR (*Activity* means muscle tone, *Pulse* means heart rate, *Grimace means* response to smell or foot slap, *Appearance means* color and *Respiration means* breathing) score.
2. Neonates with any congenital malformations, syndromes, or other congenital diseases that could affect the outcome measures.
3. Breach presentation.
4. High risk pregnancy.

5. Cesarean sections.
6. Anemic, diabetic, hypertensive, smoker mothers were excluded from this study.
7. Women who have given birth to a pre-term infant and multiple pregnancies were also excluded from this study.

Exclusions 2 and 3 were due to the lack of control over the timing of cord clamping in these conditions.

Randomization was done on admission to the labor room, when the women were in the first stage of labour. Women who fulfill the inclusion criteria and who agree to participate in study were entered in sequential manner. They were randomized in to two groups each having 150 patients by using random number tables.

Group A (150 Ladies) was subjected to early cord clamping (ECC) with in 20 sec of delivery, and Group B (150 Ladies) was subjected to delayed cord clamping (DCC) at three minutes interval after delivery.

After Spontaneous vaginal birth all infants were placed approximately 10 centimeter below the vaginal introitus, dried and wrapped in worm towel. The infant remained in this position until cord was clamped. The blood sample was collected from the cut end of the cord of new born for Hb (g/dl), packed cell volume and serum billirubin estimation. Cord Blood was collected in EDTA tubes for complete blood count, and in serum separator tubes for estimation of serum ferritin status, serum bilirubin.

After the delivery, the babies were cared for according to clinical routines, and early breast feeding was encouraged.

Infants stayed at the postnatal ward with their mothers for two or three days, except whom to leave the hospital earlier and infants who were admitted to the neonatal unit. All infants were examined by a physician during the first 72 hours, in accordance with clinical routines.

The infants were scheduled for three month for follow-up visits. The blood samples were collected by butterfly needles (BD) gauze 23 – 24. Complete blood counts were analyzed with an automated hematology analyzer (Sysmex XT – 4000 *i* Japan). Serum ferritin and bilirubin were analyzed with Beckman Coulter CX – 5 Pro USA).

Types of Interventions

1. Early cord clamping, defined as application of a clamp to the umbilical cord before 60 seconds of the birth of the infant.
2. Delayed cord clamping, defined as application of a clamp to the umbilical cord greater than one minute after birth or when cord pulsation has ceased.

Operational Definitions

Anemia: On Cord blood after clamping, the anaemia was diagnosed when hemoglobin level by Hematological analyzer (Sysmex XT 4000i, Sysmex, Kobe, Japan) was < 14.5 g/dL and at 4 months the anaemia was diagnosed when haemoglobin < 10.5 g/dL and **Iron deficiency anemia** was diagnosed at serum ferritin < 20 µg/L.

Hyperbiliruninaemia: At the age of 2 days at serum bilirubin was 15 mg/dL by Beckman coulter CX5 Pro USA.

Polycythemia: Packed cell volume > 0.65.

Statistical analysis: SPSS version 12.0 was used to analyse data. Quantitative variable like age was presented by calculating mean and standard deviation while presence or absence of neonatal anemia in this study was presented by calculating frequency and percentage.

Results

The study was comprised of 300 mother-infant pairs (in two groups A and B) eligible for inclusion criteria; 150 were randomized to ECC (Group A) and 150 to DCC (Group B). The mothers in the both groups A and B groups were compared in terms of their age (mean age of group B; 25.5 ± 5 was greater than A: 24.3 ± 2.1), parity (47% vs 45% primigravida and 53% vs 55% Multi gravid mothers in both groups), weight (71.2 ± 13.6 Kg, group A as compared to 70.8 ± 11.8 Kg, group B) and hemoglobin level. The mean maternal (Hb) level on admission to the labour ward was higher in the ECC (11.46 ± 0.56 g/dL) group than in the DCC (11.16 ± 0.45 g/dL) group and the difference was not significant (Table 1 and 2). All the maternal baseline characteristics were not significantly different in both study groups.

Infant baseline characteristics did not differ significantly (Table 2). Low birth weight was not observed in any infant. Anemia was comparable in both groups along with all hematological findings lie Hb and Hct in both groups A and B. The frequency of anemia was greater in the group A as compared to group B, and

this difference was significant (p = 0.000). No polycythaemia was seen in any infant at birth. The Hematocrit level was significantly higher in the group B (58.3 ± .2% as compared to 61.3% ± 7.1 after 24 hours while 32.8 ± 7.1% as compared to 61.3 ± 7.1 after 48 hours). The difference was significant in both groups (p = 0.035 and 0.01 respectively). Hb levels after 24 hours showed higher values in the group B (18.7 ± 3.2 g/dL as compared to 16.5 ± 2.1 g/dL after 24 hours while 17.4 ± 2.2 g/dL as compared to 12.5 ± 4.1 g/dL after 48 hours) and these differences were statistically significant (p = 0.07 and 0.04 respectively). The serum ferritin level was also significantly higher in group B (80.75 ± 3.2 ng/mL as compared to 85.5 ± 4.2 ng/mL after 24 hours while 95.5 ± 2.1 ng/mL as compared to 55 ± 7.3 ng/mL after 48 hours) and these differences were statistically significant (p = 0.01 and 0.001 respectively) (Table 4).

There was a significant difference in the development of infants jaundice after 48 hours. The infants whose cord's bilirubin level was greater than 2.00 mg/dl developed clinical jaundice and needed phototherapy as compared to those whose level was lesser than 2.00 mg/dl within 24 hours evaluation. Whilst there were mild non-significant difference was observed in mean bilirubin level in DCC (7 ± 2.3 vs 5 ± 3.5 mg/dL in 48 hours). However a significant number of infants developed jaundice in DCC group as compared to ECC groups (8% vs 2%; p = 0.016) (Table 5).

Discussion

Early clamping of cord should be avoided in routine obstetrical practice there should be given sometime for the clamping of cord which prevent anemia over first 3 months of life and enriching iron stores and ferritin level for as long as 6 months. Although this is a particular importance for developing countries in which anemia during infancy and childhood is highly remarkable. It is likely to have an important impact on all

Table 1: Distribution of case by age (n = 300).

Age (Years)	Group A (n = 150)	Group B (n = 150)	Total (n = 300)
20 – 25	90 (60%)	93 (62%)	183 (61%)
26 – 30	47 (31%)	45 (30%)	92 (31%)
31 – 35	13 (9%)	12 (8%)	25 (8%)
Total	150	150	300
Mean ± SD age	24.3 ± 2.1	25.5 ± 1.9	25 ± 2

Table 2: Status of mothers participating in the study (n = 300).

Groups	Age		Weight		Mothers' Hemoglobin		Primi-gravida	Multi-gravida
	Mean	Range	Mean	Range	Mean	Range		
Group A (n = 150)	24.3 ± 2.1	20 – 35	71.2 ± 13.6	50 – 102	11.16 ± 0.45	10 – 14	70 (47%)	80 (53%)
Group B (n = 150)	25.5 ± 1.9	20 – 35	70.8 ± 11.8	45 – 112	11.46 ± 0.56	10.5 – 14.5	67 (45%)	83 (55%)
Statistical difference	NS		NS		NS		NS	NS

Table 3: Comparison of Neonatal Anemia between two groups after 3 months.

Groups	Gestational Age (Weeks)	Weight in Kg	Neonatal Anemia		Total
			Yes	No	
Group A (n = 150)	40.5 ± 4.5	3.6 ± 0.54	32 (21%)	118 (79%)	150
Group B (n = 150)	40 ± 4.7	3.4 ± 0.31	5 (3%)	145 (97%)	150
Total	P = 0.25	P = 0.36	0.000	0.000	300

Table 4: Comparison of neonatal Hb, haematocrit and serum Iron Level after 24 hours of birth and after 3 months.

Groups	Haematocrit (Mean)		Newborn Hemoglobin (Mean)		Newborn Ferritin (Mean)	
	Cord Blood 24 Hours (Normal Level: 55 – 68%)	3 Months (Normal Range 30 – 46%)	Cord Blood 24 Hours (Normal Range 14 – 20 g/dL)	3 Months (Normal Range: 4 – 20 g/dL)	Cord Blood 24 Hours (Normal Range: 25 to 200 ng/mL)	3 Months (Normal Range: 50 to 200 ng/mL)
Group A	58.3 ± 2.2	32.8 ± 7.1	16.5 ± 2.1	12.5 ± 4.1	80.75 ± 3.2	55 ± 7.3
Group B	61.3 ± 7.1	45.6 ± 5.6	18.7 ± 3.2	17.4 ± 2.2	85.5 ± 4.2	95.5 ± 2.1
Significance Level	P = 0.035	P = 0.01	P = 0.007	P = 0.004	P = 0.01	P = 0.001

Table 5: Hyperbilirubinaemia and need for phototherapy at 2 days old among infants.

Groups	Serum Bilirubin Level (mg/dL)					Mean Pack Cell Volume	
	48 Hours (Mean)	48 Hours (Mean)	3 Months (Mean)	Serum Bilirubin > 2.5 mg/dl (48 Hours)	Serum Bilirubin > 2.5 mg/dl (3 Months Hours)	48 Hours	3 Months
Group A	1.8 ± 1.5	5 ± 3.5	0.56 ± .0.41	4 2.6%	0	52 ± 2	32 ± 3.2
Group B	2.0 ± 2.7	7 ± 2.3	0.58 ± .0.31	13 8.6%	0	56 ± 2.1	34 ± 2.3
Significance Level		NS (p = 0.57)	NS (p = 0.68)	P = 0.016	0	P = 0.1	P = 0.1

newborns regardless of birth setting.

There was no statistical difference in the maternal baseline characteristics like, age, gestational age weight, Hb, and parity in both study groups. Hyperbilirubinaemia, polycythaemia and hyperviscosity syndrome are frequently mentioned adverse effects of placental transfusion and in infants with DCC.[9]

The major objective of this study was to evaluate whether ECC leads to anemia and DCC could improve the haematological status of infants. The difference we found in the mean Hemoglobin and Hematocrit levels of infants at 24 hours after delivery in favor of the DCC group is possibly of clinical importance. We found a difference in the mean Hemoglobin and Hematocrit levels of infants at 24 hours and 48 hours after delivery in favor of the DCC group. This difference is statistically significant and is possibly of clinical importance. This result is in accordance with earlier published studies on the short – term effects of placental transfusion.[15,16]

Delaying clamping of the cord for at least two to three minutes seems not to increase the risk of postpartum hemorrhage. Iron stores in the term newborn are normally adequate to maintain iron sufficiency for approximately four months of postnatal growth. It has been seen that late cord clamping can be advantageous for the infant by improving iron status which may have clinical value to save the infants from developing anemia.[14,17]

In our infants early cord clamping resulted in iron deficiency anemia due to decreased amount of iron stores and ferritin level. The difference was statistically significant (p = 0.01 and 0-001) during first 24 hours and after three months.

In this study 32 / 118 (21%) neonates are anemic in result of early cord clamping and mean HCT is statistically low (p = 0.035 and 0.001) after 24 hours and 3 months.

It is mentioned in many publications that DDC results in polycythemia, jaundice, postpartum haemorrhage and other maternofetal complications[18-20] but in our study no such problems were observed except hyperbilirubinemia and this difference was no doubt significant (P = 0.016) but was successfully managed by phototherapy. Therefore our findings are consistent with Mc Donald and Middletons.[14] Infants with cord bilirubin levels less than 2.0 mg/dL have only a 4 percent chance of developing hyperbilirubinemia and a 1.4 percent chance of needing phototherapy. However, if serum cord bilirubin levels are more than 2.0 mg/dL, the infant has a 25 percent chance of developing subsequent hyperbilirubinemia. Serum bilirubin level was normal at the end of 3 months and there was no statistical difference in both groups. Whilst there were mild non-significant difference was observed in mean bilirubin level in DCC (7 ± 2.3vs 5 ± 3.5 mg/dL in 48 hours). However a significant numver of infants developed jaundice in DCC group as compared to ECC groups (8% vs 2%; p=0.016). Our findings are consistent with Lanzkowsky and other authors.[18-20]

Conclusion

To get the normal hematocrit level in term infants, it is very necessary to avoid this practice to do early cord clamping and this practice should be changed in modern obstetrical practice as it is not the standard method as it is the cause of iron deficiency anemia. Delayed cord clamping method increases mean neonatal hematocrit, hemoglobins within a physiologic range and save from developing iron deficiency anaemia although delaying clamping increases the risk of jaundice requiring phototherapy.

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Future Plan: More studies need to be carried out to look for the further hazards of early and delayed cord clamping and also it is necessary to know the exact timings of cord clamping as it is a big obstetrical issue now a days. The obstetrician should be particular regarding during crod clamping they should weight till the cord pulsation in the cord may felt.

Recommendations

1. Delayed Cord clamping criteria should be encouraged (1 – 3 minutes) and leaving the cord to pulse does not causes any problem but improves the iron status of the infant.
2. If you can think about what Nature intended, our

ancestors way back before scissors and clamps were invented must have had to wait to deal with the cord/placenta until the placenta was birthed. They probably chewed it, ground it with rocks, or burned it through with hot sticks from the fire. The little teeth on the clamps indicate the traumatizing of the vessels is necessary to quell bleeding.

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