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Effect of delayed versus early cord clamping on hemoglobin level of neonates born to anemic mothers

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ABSTRACT

Introduction: In common obstetric practice, the cord is clamped soon after birth. Deferring cord clamping for 2–3 minutes after birth or when cord pulsations stop allows blood flow between baby and placenta to continue for a few moments. Recent research provides evidence for the beneficial effect of delayed cord clamping (DCC) on infant iron status and hemoglobin (Hb) levels. Iron deficiency anemia is a major public health problem in young children worldwide. The increase in neonatal blood volume seen with DCC has the potential both to increase iron stores and Hb concentrations. This study is conducted as the anemia is highly prevalent among the pregnant females in Pakistan; thus, they are likely to reproduce children with low Hb levels. Presently, early cord clamping (ECC) is a common practice in labor suites across Pakistan, but hypothetically speaking, huge benefits were anticipated from delayed clamping.

Methodology: All patients fulfilling the inclusion and exclusion criteria were selected from Labor Room/Emergency Department of the hospital. The patients were not aware of the randomization arm and were selected via lottery method. All patients underwent spontaneous vaginal delivery and informed consent was taken for taking baby's blood sample within 24 hours after birth. DCC/ECC was done according to randomization. Blood sample of the neonates was sent to a standard laboratory within 24 hours after birth for analyzing full blood counts.

Results: The average neonatal Hb(NHb) level in Group A (DCC) was 18.7 mg/dl and the range was 16.2–19.8 mg/dl but in Group B (ECC) the average NHb level was 17.6 mg/dl and the range was 16.7–19.2 mg/dl. The calculated "*t*" value is 8.290 ($p = 0.000$) and thus shows statistically significant difference between the two groups. Hence alternative hypothesis is accepted.

Conclusion: Our study supports that delaying cord clamping to >180 seconds in low- and middle-income countries, where iron deficiency anemia is prevalent among mothers and newborns, may be beneficial as it improves NHb. Thus, delayed clamping of cord should become a standard protocol in obstetrical practice due to its proven benefits over early clamping of cord.

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Introduction

The management of the umbilical cord in complex situations is inconsistent between birth settings [1]. A brief delay in clamping the umbilical cord after birth offers health benefits to the newborn, with no adverse effects to the mother or her infant [2]. Yet, in most obstetric practice, the cord is clamped soon after birth [2]. Deferring cord clamping allows blood flow between baby and placenta to continue for a few moments [3]. In the term infant, although this may result in an increase in iron stores thereby decreasing the risk of anemia, it may adversely increase the risk of jaundice and the need for phototherapy [4].

Clamping and cutting of the umbilical cord at birth is the oldest and most prevalent intervention

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in humans [5]. In spite of that, the optimal timing of umbilical cord clamping has been debated in the scientific literature for at least the last century when cord clamping practices shifted from delayed towards immediate clamping [6]. Recent research provides evidence for the beneficial effect of delayed cord clamping (DCC) on infant iron status and hemoglobin (Hb) levels [6].

Iron deficiency anemia is a major public health problem in young children worldwide [7] and can lead to neurologic issues in older children including poor school performance, decreased cognitive abilities, and behavioral problems [5]. Delayed umbilical cord clamping has been suggested as a measure to prevent infant iron deficiency [7].

Placental transfusion is the transfer of blood between the placenta and the baby at birth [8]. For term births, this blood flow is usually complete by 2 minutes, but may continue for up to 5 minutes [8]. The mean volume of placental transfusion for term births is 100 ml, which is around 29 ml/kg birth weight and 36% of neonatal blood volume at birth [8]. DCC, usually defined as ligation of the umbilical cord 2–3 minutes after birth or when cord pulsations stop, will thus result in a larger placental transfusion than early cord clamping (ECC) performed immediately after delivery [7].

This study was conducted as anemia is highly prevalent among the pregnant females in our local population; thus, they are likely to reproduce children with low Hb levels. A study done in Pakistan reported that 138 (55%) out of 250 women were anemic, in that 83 (60%) were moderately anemic and 55 (40%) had mild anemia [9]. Anemia is more common in Pakistan particularly in women with no previous antenatal checkup, and it is more common in women of low socio-economic group [10]. Presently, ECC is a common practice in labor suites across Pakistan; and no significant local data is available on the effect of DCC on neonatal hemoglobin (NHb), where hypothetically speaking huge benefits are anticipated.

Materials

This study was conducted in the Department of Gynae Unit-I, Jinnah Hospital Lahore. The duration of study was from August 17, 2015 to January 10, 2016. One hundred patients with 50 in each group were enrolled. Group A included neonates who underwent DCC and Group B included neonates who underwent ECC.

Inclusion Criteria

- Pregnant mothers aged 18–40 years.
- Only neonates born by spontaneous vaginal delivery.
- Mothers with Hb level ≤ 9 g/dl.

Exclusion Criteria

- Neonates who needed emergency resuscitation.
- Neonates delivered by cesarean section.
- Pre-term births. [gestational age (GAge) ≤ 37 weeks on last menstrual period].
- Neonates with congenital anomalies. (on ultrasound & clinical examination).

Methods

Sampling technique used was non-probability consecutive sampling. Data were collected by filling licensed questionnaire. Total calculated data were original and self-measured. We explored numerous databanks like PubMed, Trip databases, clinical queries, and also published articles and guidelines from multiple societies of Obstetricians and Gynecologists. We calculated the results by running software "SPSS 21."

Data Collection Method

All patients, fulfilling the inclusion and exclusion criteria, were selected from Labor Room/Emergency Department of hospital. The patients were not aware of the randomization arm and were selected via lottery method. All patients underwent spontaneous vaginal delivery and informed consent was taken for taking baby's blood sample within 24 hours after birth. All procedures were done by skilled post graduate obstetric residents. DCC/ECC was done according to patient's randomization and study protocol. Blood sample of all neonates were drawn by an expert phlebotomist within 24 hours after birth and transferred to same standard laboratory for complete blood count. Results were analyzed when the report was received from the laboratory.

Results

Demographic data from my research shows that majority of mothers were in the age group of 22–35 years and mean maternal age (MAge) was 26.66 ± standard deviation (SD) 4.66. Mean maternal Hb (MHb) was 8.6 ± SD 0.51, and MHb varies from 6 to 9 mg/dl. It demonstrates that all mothers of our

Table 1. Case summaries.

Group		NHb	MHb	MAge	GAge	NBW	NAS
Group A	*N*	50	50	50	50	50	50
	Mean	18.702	8.596	26.54	274.70	3.094	8.64
	SD	0.7506	0.4789	4.441	7.538	0.3425	0.485
	Minimum	16.2	6.6	18	261	2.5	8
	Maximum	19.8	9.0	37	289	4.0	9
Group B	*N*	50	50	50	50	50	50
	Mean	17.584	8.622	26.78	275.34	3.270	8.66
	SD	0.5881	0.5512	4.929	6.945	0.3138	0.519
	Minimum	16.7	6.4	18	259	2.6	7
	Maximum	19.2	9.0	40	288	4.0	9
Total	*N*	100	100	100	100	100	100
	Mean	18.143	8.609	26.66	275.02	3.182	8.65
	SD	0.8750	0.5139	4.669	7.218	0.3386	0.500
	Minimum	16.2	6.4	18	259	2.5	7
	Maximum	19.8	9.0	40	289	4.0	9

NHb = neonatal hemoglobin, MAge = maternal age, MHb = maternal hemoglobin, GAge = gestational age, NBW = neonatal birth weight, NAS = neonatal APGAR score.

Table 2. Group statistics (comparison of Hb levels between Group A and Group B).

	Group	*N*	Mean	SD	Standard error mean	*t* and *p* value
NHb	Group A	50	18.702	0.7506	0.1062	$t = 8.290$
	Group B	50	17.584	0.5881	0.0832	$p = 0.000$

NHb = neonatal hemoglobin. *P* value calculated is >95%.
Comparison of Hb levels between DCC and ECC groups.

Table 3. Stratification of mean Hb level between both DCC and ECC groups with respect to MAge ($X = 100$).

Mage (years)	Groups	*X*	Mean ± SD	*P* value
18–30	A	42	25.0 ± 2.8	0.48
	B	44	25.5 ± 3.5	
31–40	A	8	34.3 ± 1.8	0.19
	B	6	36.3 ± 2.9	

sample population were anemic as per the inclusion criteria of our research protocol. Maternal GAge was between 259 and 289 days and mean maternal GAge was 275 ± SD 7.2. Neonatal birth weight was 2.5–4 kg approximately equal in both Group A and Group B and mean was 3.2 ± SD 0.34.The average NHb level in Group A (DCC) was 18.7 mg/dl (range was 16.2–19.8 mg/dl) but in Group B (ECC) average NHb level was 17.6 mg/dl (range was 16.7–19.2 mg/dl) as shown in (Table 1).

The calculated "*t*" value for comparison between Hb levels in neonates of Group A and B is 8.290 ($p = 0.000$) and shows significant difference between the two groups (Table 2), Hence alternative hypothesis is accepted.

In our study, we divided the MAge into two Stata 18–30 years and 31–40 years. In first Stata, mean MAge in Group A is 25 ± 2.8 ($x = 42$) and in Group B, 25.5 ± 3.5 ($x = 44$) with *p* value 0.48. In second Stata, *p* value is 0.19 with mean MAge of Group A is 34.3 ± 1.8 ($x = 8$) and Group B is 36.3 ± 2.9 ($x = 6$) (Table 3).

Appearance, pulse, grimace, activity, and respiration (APGAR) score vary from 7 to 9 and mean is 8.65 ± SD 0.5. As shown in pie chart, neonates 18 (36%) have normal APGAR score and 32 (64%) have low APGAR score in Group A, but in Group B neonates 16 (32%) have normal APGAR score and 34 (68%) have low APGAR score. It shows that the DCC may positively affect APGAR score of neonate (Fig. 1) but the relationship was non-significant ($p > 0.05$).

We make two groups of maternal gestational age. In first group, GAge was between 259 and 275 days, and in second group, it ranges between 276 and 289 days. In first group, Group A ($x = 26$) has mean maternal GAge of 268 ± 4.4 and Group B ($x = 20$) has 267.8 ± 4.4 with *p* value 0.54. In second group, mean maternal GAge in Group A ($x = 24$) was 281.3 ± 3.8 and in Group B ($x = 30$) was 280.1 ± 3.0 (Table 4).

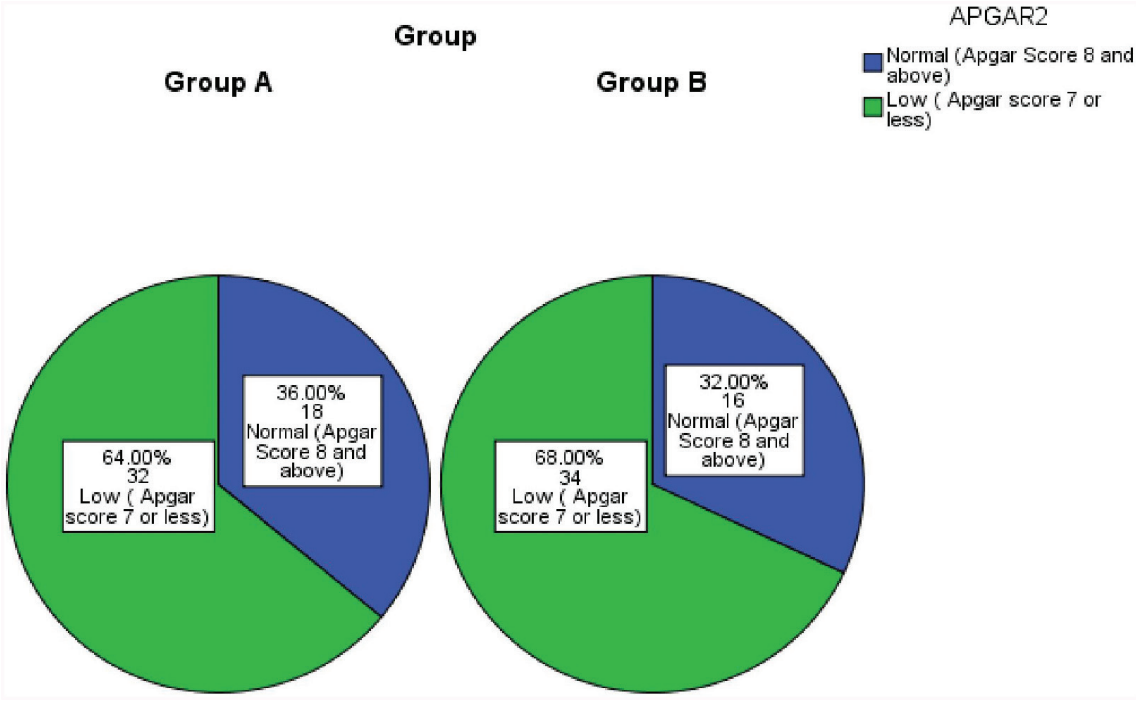

Figure 1. Pie chart showing APGAR scores in individual groups.

Table 4. Stratification of mean Hb level between both DCC and ECC groups with respect to gestational age (*X* = 100).

Geatational age (days)	Groups	*X*	Mean ± SD	*P* value
259–275	A	26	268.7 ± 4.4	0.54
	B	20	267.8 ± 4.4	
276–289	A	24	281.3 ± 3.8	0.23
	B	30	280.1 ± 3.0	

Table 5. Stratification of mean Hb level between both groups with respect to birth weight (*X* = 100).

Birth weight (kg)	Groups	*X*	Mean ± SD	*P* value
2.5–3.0	A	30	2.8 ± 0.2	0.99
	B	13	2.8 ± 0.1	
3.1–4.0	A	20	3.4 ± 0.06	0.87
	B	37	3.4 ± 0.04	

In Table 5, we describe the birth weight division into 2.5–3.0 kg and 3.0–4.0 kg. In first division, *p* value was 0.99 with mean fetal birth weight of Group A was 2.8 ± 0.2 (*x* = 30) and Group B was 2.8 ± 0.1 (*x* = 13). In second division, Group A (*x* = 20) has mean birth weight 3.4 ± 0.06 and Group B (*x* = 37) has 3.4 ± 0.04 with *p* value of 0.87.

Discussion

The time to umbilical cord clamping may have important impact on a population's health, as shown by the results in this thesis and previous data. It is estimated that approximately 3.6 billion people on Earth are iron deficient and 2 billion of them have overt iron deficiency anemia [11]. Iron deficiency anemia is also highly prevalent in women of child-bearing age group and children below 5 years of age in low- and middle-income countries like Pakistan where we conducted the study. In parts of the world where maternal iron deficiency anemia is prevalent, up to 30% of infants also suffer from iron deficiency anemia. In the developed nations, iron deficiency is prevented by iron supplementation. Many research papers published over last few decades have endorsed that delayed umbilical cord clamping at birth enhances red cell mass and improves iron stores during infancy [12–15]. Nature intends babies to get most of the iron they'll

need for their early development from the placental blood reservoir, rather than from mother, as little iron goes into breast milk [7].

The comparative risks and benefits of ECC *vs*. DCC in the term and preterm neonate remain unclear that who is particularly more at risk for anemia and various neonatal morbidities and mortality as compared to those who are born at term [16].

In infants born at term, 1 minute delay in cord clamping after delivery leads to an additional 80 ml of blood to flow from the placenta to the infant's circulation, which increases to about 100 ml if waited for 3 minutes before clamping the cord. This additional blood increases body iron stores, amounting to 40–50 mg/kg of body weight which when added to approximately 75 mg/kg of body iron present at birth in a full-term newborn, which helps in preventing iron deficiency during the first year of life [17]. There is enough data available to support that in term infants delaying the cord clamping results in higher Hb/hematocrit levels immediately after birth, which persists up to 4–6 months of age [17–19]. The mean Hb was found to be 2–3 g/dl higher in the DCC group and our results are also consistent with this finding. Another study proved that the ferritin levels remained higher in infants in the late clamping group until 6 months: weighted mean difference, +11.8 μg/l [95% confidence interval (CI), 4.07–19.53] [17].

Yasmeen et al. proved that that there is significantly high Hb, iron, and ferritin levels in DCC group. The results of Hb, serum iron, and ferritin levels at 24 hours of age in early clamping group were 16.53 (±2.13) g/dl, 52.20 (±38.78) μg/dl, and 127.63 (±57.45) μg/l, these parameters in delayed clamping group were 18.65 (±2.08) g/dl, 84.35 (±35.03) μg/l, and 188.88 (±107.58) μg/l, respectively. These results were significant with the p value of <0.05 [20]. Our study also concluded that delaying the cord clamping for 3 minutes significantly improves the NHb levels during first 24 hours.

Some clinicians still raise the query about the relationship between DCC and polycythemia, hyperbilirubinemia, and phototherapy requirements though none of the studies of DCC have reported an increased risk as compared to the early clamping group. The authors of a meta-analysis of 1,762 infants concluded a significantly higher rates of phototherapy [relative risk (RR), 1.69; 95% CI, 1.08–2.63] and clinical jaundice [15] in infants in the DCC group. However, indications for phototherapy in different research papers were not reported. Moreover, the research papers that reported polycythemia did not report simultaneously the increased need for phototherapy. The studies which reported increased need of phototherapy also reported that there were similar levels of bilirubin in the early and DCC group.

In a group of infants, cord milking has also been studied as an alternative to DCC with positive results [21–23]. In umbilical cord milking, the unclamped umbilical cord is grasped and blood is pushed toward the infant several times before it is clamped. This procedure only takes 20 seconds [24]. A recent meta-analysis of seven randomized controlled trials of umbilical cord milking in premature infants (<33 weeks) demonstrated that these infants have higher Hb and a lower risk for oxygen requirement at 36 weeks as compared with those who undergo immediate cord clamping [25]. Another randomized controlled trial demonstrated higher systemic blood flow with cord milking in preterm neonates compared with delayed clamping [26].

DCC seems to be a safe alternative when handling asphyxiated newborns after i.e., nuchal cord and shoulder dystocia [27], as the placenta could potentially supply the newborn with fresh, oxygenated, and glucose-rich blood as well as a high concentration of stem cells.

There is a study that evaluated the feasibility of neonatal resuscitation when the cord is still attached to the placenta, this study also measured infant blood volume and interestingly concluded that DCC resulted in higher blood volumes [28]. The advantages of DCC also include a reduced need for blood transfusions for treating low blood pressure (RR, 0.39; 95% CI, 0.18–0.85) and anemia (RR, 0.49; 95% CI, 0.31–0.81) [29]. Preterm newborns (under <37 weeks' gestation) in a systematic review of 10 trials (sample size 454) of ECC *vs*. DCC showed no statistically significant differences between the groups in cord blood pH (weighted mean difference, 0.01; 95% CI, −0.03–0.05), APGAR scores (RR for 5 minutes APGAR < 8, 1.17; 95% CI, 0.62–2.20), and temperature on admission (weighted mean difference, 0.14°C; 95% CI, −0.31–0.03) [30]. We only studied APGAR scores in addition to NHb but the results were statistically non-significant.

Conclusion and Recommendations

Our study and many other recently conducted studies worldwide support that delaying cord clamping to >180 seconds in low- and middle-income

countries, where iron deficiency anemia is prevalent among mothers and newborns, may be beneficial as it significantly improves NHb.

In addition, there does not appear to be any significant difference between infants receiving ECC *vs*. DCC with respect to APGAR scores.

Thus, we recommend that where delayed clamping of cord should become a standard protocol in obstetrical practice due to its proven benefits over early clamping of cord, future research is also needed to set down guidelines explaining and answering certain questions such as what is the optimum delay to clamp the cord? Are there differential benefits between milking and delayed clamping? Role of delayed clamping in C-section deliveries?

Competing Interests

The authors declare no conflict of interest.

Ethical approval

Ethical approval was obtained from the Clinical Research Ethics Committee of the Jinnah Hospital Lahore/Allama Iqbal Medical College in April' 2014.

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