The Egyptian Journal of Hospital Medicine (October 2019) Vol. 77 (1), Page 4700-4704

Early Versus Delayed Umbilical Cord Clamping in Preterm Births

Tarek Ramadan Abbas, Adel Aly Elboghdady, Mohammed Elnady Abdel Samea Mohammed *
Department of Obstetrics and Gynecology, Faculty of Medicine – Al-Azhar University
***Correspondence author:** Mohammed Elnady Abdel Samea Mohammed,
Mobile: (+20) 01146211085, **E-mail:** m.elnady65@yahoo.com

ABSTRACT0020
Background: Preterm infants are at a great risk for both cognitive and motor delay. Hypovolemia secondary to immediate cord clamping, may be disruptive to the developing brain resulting in subsequent motor delay.
Objective: The aim of this work is to compare early versus delayed cord clamping in cases of preterm birth.
Patients and Methods: This is a prospective randomized controlled study which was performed at Al-Azhar University Maternity Hospital from July 2018 to February 2019. It included 100 pregnant patients. They were divided into two equal groups: Group I with early cord clamping (ECC). Group II with delayed cord clamping (DCC).
Results: In our study the hematocrit on day 1 was also significantly higher in the DCC group (5.2%+50.8 ±vs. 58.5 ±5.1 %, p value 0.00). The DCC group required significantly longer duration of phototherapy (55.3±40.0 h vs. 36.7±32.6 h, p value 0.016) and had a trend towards higher risk of polycythemia probably due to the higher hemoglobin and bilirubin pool in those babies, however the incidence of significant jaundice was not different. In this study, there was no statistically significant difference in blood pressure between neonates of both groups of ECC and DCC. Our study found that 24% of the group underwent delayed cord clamping needed blood transfusion versus 70% of infants of the group of the immediate cord clamping.
Conclusion: Delayed cord clamping (DCC) (more than 30 seconds) in preterm births is associated with higher Hb, hematocrit and less need for blood transfusion compared to immediate cord clamping.
Keywords: Umbilical cord, DCC, ECC, Preterm Births.

INTRODUCTION

Although the mortality rate for preterm infants and the gestational age-specific mortality rate have dramatically improved over the last 3 to 4 decades, infants born preterm remain vulnerable to many complications [(1)]. Anemia of prematurity is a common problem seen in almost all preterm neonates. The placenta is a reservoir of fetal blood, which could be useful to the neonate [(2)].

The development of anemia of prematurity is due to inadequate RBC production, shortened RBC life span and blood loss due to frequent samples of blood that obtained for various tests. These losses are often 5-10% of the total blood volume esp. premature babies who are liable to NICU admission and more frequent visits for follow up. Studies on harvesting of placental blood indicate that the placenta can contain up to 40% of the total circulating fetal blood volume, with perhaps 15 to 20 mL being situated in the cord vein [(3)]. Consequently, the timing of the clamping of the cord {more specifically, early cord clamping (ECC) versus delayed cord clamping (DCC)} has been the subject of much debate [(2)].

Delayed umbilical cord clamping appears to be beneficial for term and preterm infants. In term infants, delayed umbilical cord clamping increases hemoglobin levels at birth and improves iron stores in the first several months of life, which may have a favorable effect on developmental outcomes. There is a small increase in jaundice that requires phototherapy in this group of infants. Consequently, health care providers adopting delayed umbilical cord clamping in term infants should ensure that mechanisms are in place to monitor for and treat neonatal jaundice [(4)].

In preterm infants, delayed umbilical cord clamping is associated with significant neonatal benefits, including improved transitional circulation, better establishment of red blood cell volume, decreased need for blood transfusion, and lower incidence of necrotizing enterocolitis and intraventricular hemorrhage. Delayed umbilical cord clamping was not associated with an increased risk of postpartum hemorrhage or increased blood loss at delivery, nor was it associated with a difference in postpartum hemoglobin levels or the need for blood transfusion [(5)].

AIM OF THE WORK

The aim of this work is to compare early versus delayed cord clamping in cases of preterm birth.

PATIENTS AND METHODS

This is a prospective randomized controlled study which was performed at Al-Azhar University Maternity Hospital from July 2018 to February 2019. It included 100 pregnant patients.

The study population was divided into two equal groups: Group I with early cord clamping (50 patients). Group II with delayed cord clamping (50 patients).

Inclusion criteria:

Patients delivered before 37 completed weeks of gestation either vaginally or by cesarean section.

Exclusion criteria:

- Antepartum hemorrhage.
- Multiple pregnancies (twins and more).
- Fetal hydrops.
- Rhesus isoimmunization.
- Major congenital anomalies.
- Early neonatal sepsis.

Received:1/7/2019
Accepted:1/8/2019

- Medical disorders of the mother (e.g. D.M.).

All patients were subjected to:

- Antenatal consent
- Complete history taking.
- General examination.
- The gestational age assessment using last menstrual period and/or early pregnancy ultrasound was used to establish eligibility for the study.
- The subjects were randomized using 100 opaque consecutively numbered envelopes into two equal groups: Group A with immediate cord clamping (ICC), where the umbilical cord was clamped within 15 seconds from delivery. Group B (delayed cord clamping), where the umbilical cord was clamped beyond 30 seconds till 45 seconds maximally (late clamping) from delivery.
- Neonates were held in a sterile towel or blanket approximately 10 to 15 inches below the mother's introitus at vaginal delivery or below the level of the incision on maternal abdomen or between her legs at cesarean section. Care was taken that no tension or traction was placed on the cord. A stopwatch was used to mark the time when the neonates' buttocks were delivered from the vagina or the uterus (or head if breech)
- Preterm neonates clinical data, as APGAR Score, blood pressure, temperature, jaundice, pallor and cyanosis and respiratory distress syndrome were collected by the attending neonatologist.
- Preterm neonatal laboratory results (hemoglobin, hematocrit, evidence of any neonatal sepsis as blood culture or C-reactive protein, ABG) were collected within 4 hours of age, initial serum bilirubin was collected at 12 hours of age then to be repeated at day 3 and day 7 of birth for follow up**.** Cranial ultrasound (CUS) readings used for diagnosis of intraventricular hemorrhage. CUS were read by a single pediatric radiologist who was blinded to the infant's grouping.

Ethical approval:

The study was approved by the ethics committee in Al-Azhar University Hospitals (El-Hussein and Sayed Galal) and a written informed consent was obtained from each pregnant female.

Statistical analysis

Data were analyzed using Statistical Program for Social Science (SPSS) version 20.0. Quantitative data were expressed as mean± standard deviation (SD). Qualitative data were expressed as frequency and percentage.

The following tests were done:

- Independent-samples t-test of significance was used when comparing between two means.
- Mann Whitney U test: for two-group comparisons in non-parametric data.
- Chi-square (X^2) test of significance was used in order to compare proportions between two qualitative parameters.
- Pearson's correlation coefficient (r) test was used for correlating data.
- Probability (P-value)
- P-value <0.05 was considered significant.
- P-value <0.001 was considered as highly significant.
- P-value >0.05 was considered insignificant.

RESULTS

All neonates included in this study were preterm neonates with gestational age before 37 weeks, free from pallor or cyanosis with negative CRP.

Fig 1: shows no statistically significant difference between mothers of both groups as regard age.

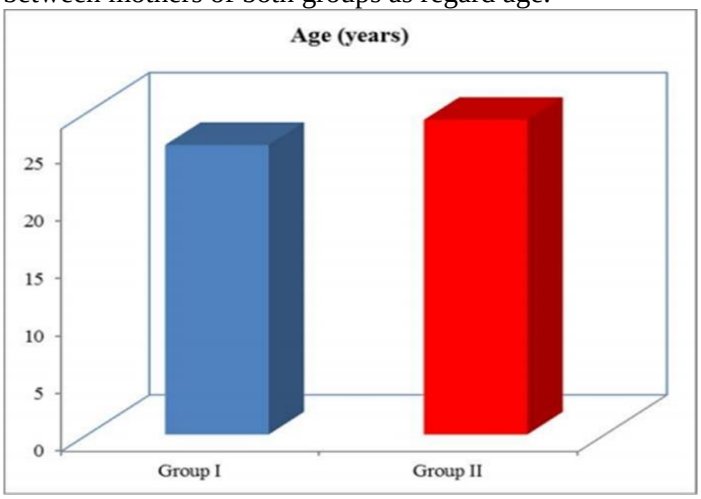

Figure (1): Bar chart between mothers of both groups according to age (years).

As regards the Apgar score of the neonates of both participating groups in this study, Table 1 shows no statistically significant difference between them in 1- and 5-minutes score after birth.

Table (1): Comparison between groups as regards Apgar score.

Apgar score	Group I	Group II	Z	p-value
1 min. Median (IQR) Range	6 (1) 5-7	6 (1) 5-7	0.073	0.787
5 min. Median (IQR) Range	7.5 (1) 7-9	8 (1) 7-9	1.093	0.055

z-Mann-Whitney test

Concerning the incidence of respiratory distress syndrome, Table 2 shows there was no statistically significant difference between the neonates in the delayed cord clamping group and the neonates of the immediate cord clamping one.

Table (2): Comparison between both groups as regards respiratory distress syndrome grades I, II, III incidence.

Respiratory Distress Syndrome	Group I	Group II	Chi-square	p-value
I	16(32.0%)	27(54.0%)	4.961	0.084
II	26(52.0%)	18(36.0%)		
III	8(16.0%)	5(10.0%)		
Total	50 (100%)	50 (100%)		

Chi –square test

The arterial blood gases of preterm infants were not significantly different statistically between the two groups as shown Table 3.

Table (3): Comparison between the two groups regarding the arterial blood gases test.

Arterial Blood Gases	Group I	Group II	Chi-square	p-value
Abnormal	30(60.0%)	27(54.0%)	0.367	0.545
Normal	20(40.0%)	23(46.0%)		
Total	50 (100%)	50 (100%)		

Chi –square test

Table 4 shows highly statistically significant difference between both groups as regards HGB and HCT with higher levels with newborns who were offered delayed cord clamping.

Table (4): Comparison between groups according to hemoglobin level and hematocrit value.

	Group I	Group II	t-test	p-value
HGB				
Mean±SD	15.65±0.93	18.33±0.71	6.367	<0.001
Range	14-18	17.1-19.9		
HCT				
Mean±SD	39.97±1.64	46.33±1.51	5.958	<0.001
Range	36.1-43.7	42.2-49.1		

t- Independent Sample t-test

Table 5 shows the difference between the effect of different modulations of cord clamping concerning serum bilirubin at day 1,3 and 7. There were no significant statistical difference between neonates of both groups.

Table (5): Comparison between both groups as regards serum bilirubin level of preterm newborns at day 1,3 and 7.

	Group I	Group II	t-test	p-value
S BILL 1				
Mean±SD	5.16±0.72	5.08±0.51	0.412	0.523
S BILL 3				
Mean±SD	10.65±1.39	11.31±1.23	1.069	0.066
S BIL 7				
Mean±SD	6.22±1.20	6.09±0.80	0.380	0.539

t- Independent Sample t-test

Table 6 shows that although intracranial hemorrhage was encountered in double the number of newborns in whom early cord clamping was done (36.0% versus 18.0%), yet the difference didn't reach statistical significance (P:0.053).

Table (6): Comparison between both groups as regards incidence of intracranial hemorrhage with preterm infants.

ICH	Group I	Group II	Chi-square	p-value
Negative	32(64.0%)	41(82.0%)	3.11	0.053
Positive	18(36.0%)	9(18.0%)		
Total	50 (100%)	50 (100%)		

t- Independent Sample t-test

In table 7, Chi-square test showed highly statistically significant difference between both groups as regards the need for blood transfusion with higher rate of blood transfusion with preterm newborns who were offered immediate cord clamping.

Table (7): Comparison between both groups regarding the need of preterm newborns for blood transfusion.

Blood	Group I	Group II	Chi-square	p-value
Positive	35(70.0%)	12(24.0%)	21.236	<0.001
Negative	15(30.0%)	38(76.0%)		
Total	50 (100%)	50 (100%)		

DISCUSSION

This study demonstrated that delay in cord clamping after birth for 30 to 45 seconds results in better neonatal hemoglobin (mean 18.33±0.71 versus 15.65±0.93 in the early clamping group) and better hematocrit values 1.51+46.33 versus 39.97±1.64 in the group of early cord clamping.

In study of **Ashish *et al.*** [6] of 540 infants (281 boys [52.0%] and 259 girls [48.0%]; mean [SD] gestational age, 39.2 [1.1] weeks), 270 each were randomized to the delayed and early clamping groups. At 8 months of age, 212 infants (78.5%) from the delayed group and 188 (69.6%) from the early clamping group returned for blood sampling. After multiple imputation analysis, infants undergoing delayed clamping had higher levels of hemoglobin (10.4 vs 10.2 g/dL; difference, 0.2 g/dL; 95%CI, 0.1 to 0.4 g/dL).

Delayed cord clamping also reduced the prevalence of anemia (hemoglobin level <11.0 g/dL) at 8 months in 197 (73.0%) vs 222 (82.2%) infants (relative risk, 0.89; 95%CI, 0.81-0.98; number needed to treat [NNT], 11; 95%CI, 6-54). At 8 months, the risk for iron deficiency was reduced in the delayed clamping group in 60 (22.2%) vs 103 (38.1%) patients (relative risk, 0.58; 95%CI, 0.44-0.77; NNT, 6; 95%CI, 4-13). At 12 months, delayed cord clamping still resulted in a hemoglobin level of 0.3 (95%) CI, 0.04-0.5) g/dL higher than in the early cord clamping group and a relative risk for anemia of 0.91 (95%CI, 0.84-0.98), resulting in a NNT of (95%) 12 CI, 7-78.

In the study of Rabe *et al.* [5] which was a prospective observational study including 123 preterm infants born before 37 weeks of gestation between June

2012 and June 2013 and hospitalized at birth. Delayed cord clamping was performed for at least 30s after birth; otherwise, it was evaluated as early cord clamping. With exclusion of twin-to-twin transfusion syndrome, congenital abnormalities, alloimmunization, and perinatal asphyxia. Delayed umbilical cord clamping was performed on 79 infants and 44 infants had early umbilical cord clamping. The two groups had similar baseline characteristics. Preterm infants in the delayed cord-clamping group had a higher level of hemoglobin during the first 24h of life (17.9) g/dL versus 16.6g/dL, P=0.005), fewer of them required transfusion (14%) versus 35%, P=0.03), and fewer presented late-onset sepsis (8% versus 26% ,P=0.02) or bronchopulmonary dysplasia (9% versus 26%, P=0.03).

There was no statistically significant increase of hyperbilirubinemia requiring phototherapy **(5).**

Many other randomized controlled trials followed by meta-analysis confirm higher hematocrit values at birth and decreased rate for blood transfusion during hospitalization with delayed cord clamping **(5, 7).** These results are consistent with our study as a result of providing the neonate more time to continue blood flow from placenta until the neonate can cope with the physiological conversion from the fetal to the new neonatal blood circulation. This is correlated with studies on harvesting of placental blood that indicated that the placenta can contain up to 40% of the total circulating fetal blood volume, with perhaps 15 to 20 mL being situated in the cord vein **(3).**

In this current study, there was no statistical difference between neonates of both groups in serum bilirubin level at day 1 (mean 5.16±0.72 in early group versus 5.08±0.51 in delayed group); at day 3 (mean 10.65±1.39 in early group versus 11.31±1.23 in group of delayed cord clamping); at day 7 mean 6.22±1.20 versus 6.09±0.80 in delayed group.

In the study of **Vain *et al.* (8);** which was a randomized controlled trial that was conducted in the delivery room and neonatal intensive care unit of a tertiary hospital. One hundred preterm infants born between 30 and 36 weeks were randomized to either early or delayed cord clamping groups. Parental informed consent was obtained prior to the delivery. In the ECC group, the cord was clamped immediately after the delivery of the baby and in the DCC group; the cord was clamped beyond 2 min after the baby was delivered. Hematocrit and serum ferritin at 6 weeks of life were the primary outcomes. Incidence of anemia, polycythemia and significant jaundice were the main secondary outcomes. The mean hematocrit (27.3±3.8%vs. 31.8±3.5 %, p value 0.00) and the mean serum ferritin (136.9±83.8 ng/mL vs. 178.9±92.8 ng/mL, p value 0.037) at 6 weeks of age were significantly higher in the infants randomized to DCC group.

In our study the hematocrit on day 1 was also significantly higher in the DCC group (5.2%+50.8 ±vs. 58.5 ±5.1 %, p value 0.00). The DCC group required significantly longer duration of phototherapy (55.3±40.0 h vs. 36.7±32.6 h, p value 0.016) and had a trend towards higher risk of polycythemia probably due to the higher hemoglobin and bilirubin pool in those babies, however the incidence of significant jaundice was not different.

In this work, there was no statistically significant difference in blood pressure between neonates of both groups of ECC and DCC.

Our study found that 24% of the group underwent delayed cord clamping needed blood transfusion versus 70% of infants of the group of the immediate cord clamping.

These results differ from the study of **Ding *et al.* (9)** which was a randomized controlled trial comparing immediate (within 5 seconds of delivery) with delayed cord clamping (after 30 seconds after birth within range 31–35 seconds).

In this study, other hemodynamic tests of the two groups as APGAR score, ABG, Respiratory distress syndrome grades, blood pressure or temperature have no difference statistically between the two groups.

Iron deficiency and iron deficiency anemia are major public health problems in young children around the world and are associated with poor neurodevelopment. Young children are at particular risk due to their high iron requirements during rapid growth. Delayed cord clamping could prevent iron deficiency, but concern about jaundice has postponed the widespread introduction of delayed cord clamping **(10).**

In the present study, although intracranial hemorrhage was encountered in double the number of newborns in whom early cord clamping was done (0.36% versus 18.0%), yet the difference didn't reach statistically significance (P:0.053).

In a randomized study by **Mercer *et al.* (2);** controlled unmasked trial in which women in labor with singleton fetuses 32 > weeks' gestation was randomly assigned to ICC (cord clamped at 5–10 seconds) or DCC (30–45 seconds) groups. Women were excluded for the following reasons (their obstetrician refused to participate, major congenital anomalies, multiple gestations, intent to withhold care, severe maternal illnesses, placenta abruption or previa, or rapid delivery after admission.

In the research of **Rabe *et al.* (5)** about effect of timing of umbilical cord clamping and other strategies to influence placental transfusion at preterm birth on maternal and infant outcomes; researched randomized controlled trials comparing early with delayed clamping of the umbilical cord and other strategies to influence placental transfusion for births before 37 completed weeks' gestation. Fifteen studies (738 infants) were eligible for inclusion. Participants were between 24- and 36-weeks' gestation at birth. The maximum delay in cord clamping was 180 seconds.

Delaying cord clamping was associated with fewer infants requiring transfusions for anemia (seven trials, 392 infants; risk ratio (RR) 0.61, 95% confidence

interval (CI) 0.46 to 0.81), less intraventricular hemorrhage (ultrasound diagnosis all grades) 10 trials, 539 infants (RR 0.59, 95% CI 0.41 to 0.85) and lower risk for necrotizing enterocolitis (five trials, 241infants, RR 0.62, 95% CI 0.43 to 0.90) compared with immediate clamping.

However, the peak bilirubin concentration was higher for infants allocated to delayed cord clamping compared with immediate clamping (seven trials, 0.32 infants, mean difference 15.01 mmol/L, 95% CI 5.62 to 24.40). For most other outcomes (including the primary outcomes infant death, severe (grade three to four) intraventricular hemorrhage and periventricular leukomalacia) there were no clear differences identified between groups; but for many there was incomplete reporting and wide CIs.

With each successive publication, evidence mounts in favor of delayed cord clamping, variably defined as between 30 seconds and 3 minutes after delivery or waiting until the cord stops pulsating. The benefits, including decreased need for blood transfusions, more stable blood pressure (in preterm infants), less intraventricular hemorrhage, and decreased infections in addition to higher iron stores (still evident at 4 to 6 months, clearly outweigh the convenience factor that drives immediate clamping and cutting and the marginal increase in jaundice.

Whereas the benefits may be demonstrated in term and preterm infants, it is the preterm infants who derive the greatest benefit from delayed cord clamping. Most groups, including the World Health Organization, recommend that delayed cord clamping should be the standard practice except for emergency situations, including placental separation or major hemorrhage **(11).**

CONCLUSION

Delayed cord clamping (DCC) (more than 30 seconds) in preterm births is associated with higher Hb, hematocrit and less need for blood transfusion compared to immediate cord clamping.

RECOMMENDATIONS

- DCC should be offered to preterm births as it is associated with higher Hb and hematocrit and less need for blood transfusion.
- Further studies are needed to explore the benefits of DCC in multiple pregnancies, full term births and in certain medical disorders as diabetes mellitus.
- Further studies are needed to examine the use of uterotonics at delivery or risk of postpartum hemorrhage with DCC.

REFERENCES

1. **Symington A, Pinelli J (2006):** Developmental care for promoting development and preventing morbidity in preterm infants. Cochrane Database Syst Rev., CD001814. https://www.ncbi.nlm.nih.gov/pubmed/16625548
2. **Mercer J, Vohr B, McGrath M *et al.* (2006):** Delayed cord clamping in very preterm infants reduces the incidence of intraventricular hemorrhage and late-onset sepsis: a randomized, controlled trial. Pediatrics, 117(4):1235–1242.
3. **Brune T, Garritsen H, Witteler R *et al.* (2002):** Autologous placental blood transfusion for the therapy of anemic neonates. Biol Neonate., 81:236–43.
4. **ACOG (2013):** Committee Opinion No 579: Definition of term pregnancy. Obstet Gynecol., 122:1139-1143.
5. **Rabe H, Diaz-Rossello JL, Duley L *et al.* (2012):** Effect of timing of umbilical cord clamping and other strategies to influence placental transfusion at preterm birth on maternal and infant outcomes. Cochrane Database Syst Rev., 8:CD003248.
6. **Ashish KC, Rana N, Målqvist M *et al.* (2017):** Effects of delayed umbilical cord clamping vs early clamping on anemia in infants at 8 and 12 months: A randomized clinical trial. JAMA Pediatrics, 171(3):264-70.
7. **McDonald SJ, Middleton P, Dowswell T *et al.* (2013):** Effect of timing of umbilical cord clamping of term infants on maternal and neonatal outcomes. https://www.ncbi.nlm. nih.gov/pubme /23843134
8. **Vain NE, Satragno DS, Gorenstein AN *et al.* (2014):** Effect of gravity on volume of placental transfusion: a multicenter, randomized, noninferiority trial. Lancet, 384:235–40.
9. **Ding XX, Wu YL, Xu SJ *et al.* (2014):** Maternal anxiety during pregnancy and adverse birth outcomes: a systematic review and meta-analysis of prospective cohort studies. J Affect Disord., 159:103.
10. **Andersson O, Lindquist B, Lindgren M *et al.* (2015):** Effect of delayed cord clamping on neurodevelopment at 4 Years of Age: A randomized clinical trial. JAMA Pediatr., 169:631-8.