Early Versus Delayed Umbilical Cord Clamping in Preterm Births
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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.
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 (X²) 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).](image)

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>
<thead>
<tr>
<th>Apgar score</th>
<th>Group I</th>
<th>Group II</th>
<th>Z</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 min.</td>
<td>Median (IQR)</td>
<td>6 (1)</td>
<td>6 (1)</td>
<td>0.073</td>
</tr>
<tr>
<td></td>
<td>Range</td>
<td>5-7</td>
<td>5-7</td>
<td></td>
</tr>
<tr>
<td>5 min.</td>
<td>Median (IQR)</td>
<td>7.5 (1)</td>
<td>8 (1)</td>
<td>1.093</td>
</tr>
<tr>
<td></td>
<td>Range</td>
<td>7-9</td>
<td>7-9</td>
<td></td>
</tr>
</tbody>
</table>

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.
Although intracranial hemorrhage (ICH) (38.1%) patients (relative risk, 0.58; 95%CI, 0.36-0.89) were reduced in the delayed clamping group in 60 (95%CI, 0.81) months, delayed cord clamping still resulted in a higher rate of blood transfusion with preterm newborns who were offered immediate cord clamping.

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

<table>
<thead>
<tr>
<th>Arterial Blood Gases</th>
<th>Group I</th>
<th>Group II</th>
<th>Chi-square</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abnormal</td>
<td>30(60.0%)</td>
<td>27(54.0%)</td>
<td>0.367</td>
<td>0.545</td>
</tr>
<tr>
<td>Normal</td>
<td>20(40.0%)</td>
<td>23(46.0%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>50 (100%)</td>
<td>50 (100%)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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.

<table>
<thead>
<tr>
<th>HGB Mean±SD</th>
<th>Group I</th>
<th>Group II</th>
<th>t-test</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Range</td>
<td>15.65±0.93</td>
<td>18.33±0.71</td>
<td>6.367</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>HCT Mean±SD</td>
<td>39.97±1.64</td>
<td>46.33±1.51</td>
<td>5.958</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Range</td>
<td>36.1-43.7</td>
<td>42.2-49.1</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Chi –square 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.

<table>
<thead>
<tr>
<th>S BIL</th>
<th>Group I</th>
<th>Group II</th>
<th>t-test</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>5.16±0.72</td>
<td>5.08±0.51</td>
<td>0.412</td>
<td>0.523</td>
</tr>
<tr>
<td>3</td>
<td>10.65±1.39</td>
<td>11.31±1.23</td>
<td>1.069</td>
<td>0.066</td>
</tr>
<tr>
<td>7</td>
<td>6.22±1.20</td>
<td>6.09±0.80</td>
<td>0.380</td>
<td>0.539</td>
</tr>
</tbody>
</table>

Chi –square 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.

<table>
<thead>
<tr>
<th>ICH Group</th>
<th>Group I</th>
<th>Group II</th>
<th>Chi-square</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Negative</td>
<td>32(64.0%)</td>
<td>41(82.0%)</td>
<td>3.11</td>
<td>0.053</td>
</tr>
<tr>
<td>Positive</td>
<td>18(36.0%)</td>
<td>9(18.0%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>50 (100%)</td>
<td>50 (100%)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Chi –square 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.

<table>
<thead>
<tr>
<th>Blood</th>
<th>Group I</th>
<th>Group II</th>
<th>Chi-square</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive</td>
<td>35(70.0%)</td>
<td>12(24.0%)</td>
<td>21.236</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Negative</td>
<td>15(30.0%)</td>
<td>38(76.0%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>50 (100%)</td>
<td>50 (100%)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Chi –square test

**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 of 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...
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, 241 infants, 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 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