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Different Placental Transfusion Strategies and Their Effects on Short - Term Hematological Parameters in Term Infants

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Abstract

Background: Deferring the umbilical cord clamping produces more satisfactory neurological and hematological outcomes. Another alternative for the deferred umbilical cord clamping is the umbilical cord milking.
Objectives: This study aimed to evaluate different placental transfusion techniques in terms of hematological parameters for term neonates.
Methods: This observational study included 120 term infants assigned to groups of deferred cord clamping for 60 seconds (DCC), cut cord milking for four times with a speed of 10 cm/second (CCM), intact cord milking for four times (ICM), and a historical control group of immediate cord clamping (ICC). The primary outcome of this study was hematological parameters at birth and 24th hours. Hyperbilirubinemia, polycythemia, or respiratory distress were secondary outcomes.
Results: The median gestational ages and birth weights of neonates were 39 (37 - 40) weeks and 3270 (2365 - 4850) grams, respectively. Umbilical cord hemoglobin (Hb) and hematocrit (Hct) levels were significantly higher in the ICM group ($P < 0.01$). Hemoglobin and Hct levels at 24th hours of life were similar in DCC, CCM, and ICM groups and significantly higher than those in the ICC group ($P < 0.01$). No significant difference was found among the groups in terms of hyperbilirubinemia, polycythemia, and respiratory distress.
Conclusions: To the best of our knowledge, this study was one of the most comprehensive studies evaluating the effects of different placental transfusion strategies on hematological parameters in term infants and the first study exploring intact cord milking in term infants. Intact cord milking was suggested to be associated with higher hemoglobin levels at birth. All DCC, ICM, and CCM techniques were found to be more effective than ICC in terms of early hematological parameters.

Keywords: Placental Transfusion, Intact Cord Milking, Cut Cord Milking, Deferred Cord Clamping, Hematological Parameters

1. Background

Fetal circulation and placenta have been interesting subjects since the time of Hippocrates. In ancient cultures, the umbilical cord was not clamped unless the birth of the placenta was already completed, even if it took several hours to complete. The idea of immediate umbilical cord clamping before the completion of the placenta birth was suggested in 17th century as a simple method, and then it quickly became a routine practice. Delaying the tying and cutting of the cord until the cease of pulsation, as it occurs in nature, was re - recommended in early 19th century (1, 2).

The transfer of blood from placenta to the newborn in the period between birth and umbilical cord clamping is defined as placental transfusion which is an important factor during postnatal transition (3). Placental transfusion can be performed through different strategies such as deferred cord clamping (DCC), intact cord milking (ICM), and cut cord milking (CCM) (4). The gravity, clamping time of the umbilical cord, continuation of uterine contractions, and umbilical blood flow significantly contribute to placental transfusion volumes. However, it is known that both deferred cord clamping and umbilical cord milking (UCM) can enhance arterial oxygen content and hemodynamic stability in preterm infants; the acute effects of different placental transfusion strategies on hematological parameters in term infants had not been determined precisely (4).

2. Objectives

This study, therefore, aimed to evaluate the short - term effects of different placental transfusion strategies on early hematological parameters in term neonates.

3. Methods

This observational study was conducted between April 2019 and December 2020, and was approved by Local Ethical Committee of Istanbul Kanuni Sultan Suleyman Training and Research Hospital (2019.03.79). The inclusion criteria were as follows: (1) singleton pregnancy, (2) gestational age above 37 weeks, (3) no evidence of congenital malformations, and (4) no need for neonatal resuscitation after birth. Informed consent was obtained from all parents before birth.

Immediate umbilical cord clamping has been abandoned in our unit since 2018. Presently, the deferred cord clamping is the preferred umbilical cord management strategy, and umbilical cord milking can also be performed as unit protocol to maintain placental transfusion. Implementation of the umbilical cord management strategy depends on the decision by neonatologist according to the well - being of infant. The infants are held at introitus or thigh level during the placental transfusion in order to prevent the undesired effect of gravity. As a protocol in our unit, DCC is delayed for 60 seconds after birth, and umbilical cord milking is performed through milking for four times at 25 cm away from umbilicus with a speed of 10 cm/second for two seconds.

Infants treated with different umbilical cord management strategies were observed during the study period. Infants whose hematological parameters were assessed at birth and 24th hours of life, bilirubin levels were assessed at 24th hours of life were included to the study. A total of 120 term infants were assigned to groups according to their umbilical cord management strategies as follows: The historical control group included infants born prior to 2018 and undergoing immediate cord clamping (ICC), and DCC, CCM and ICM were the study groups. In ICC group, umbilical cord was clamped immediately after birth. The cord clamping was delayed for 60 seconds for DCC group. In CCM group, umbilical cord was clamped 25 cm away from the umbilicus immediately, then milked towards the infant over a 2 - second period with a speed of 10 cm/sec for four times. As for the ICM group, umbilical cord was not clamped but squeezed towards the infant, as it was performed in CCM group, and umbilical cord was refilled with the blood via the placental pulsations between the milking periods. Changes and differences in short - term hematological parameters (Hemoglobin [g/dL] and hematocrit (%) levels) were the primary outcomes. The presence of polycythemia at birth and the 24th hours of life, the presence of hyperbilirubinemia at the 24th hours of life, necessary phototherapy, and the presence of respiratory distress at birth were the secondary outcomes. Polycythemia was defined as having a venous hematocrit value above 65%, the presence of hyperbilirubinemia, and necessary phototherapy based on Bhutani Nomogram. Infants with ABO group or Rh incompatibility, as well as the hemolytic hyperbilirubinemia, were excluded from the study, and it was decided to explain if the umbilical cord management strategy was associated with polycythemia and hyperbilirubinemia.

Statistical analyses were performed using SPSS software 22.0 (IBM, Armonk, NY, USA). Normal distribution of variables was assessed by the Shapiro–Wilk test. Descriptive statistics were given as mean ± standard deviation (min–max) to report continuous variables and n (%) categorical variables. Mean values were compared using One - way ANOVA and Tukey HSD post hoc analysis tests, and a P - value less than 0.05 was considered significant.

4. Results

A total of 120 infants were assigned to four groups (i.e., ICC, DCC, CCM, and ICM) based on different placental transfusion strategies employed to treat them. The gestational age and birth weight of the infants were similar. The demographical characteristics of neonates are shown in Table 1.

Hemoglobin (Hb) levels at birth were comparable in ICC, DCC, and CCM groups (ICC; 16.6 ± 1.9 vs. DCC; 16.8 ± 2.4, CCM; 17.5 ± 2.4; $P > 0.05$) but were significantly higher in ICM group compared with other groups (ICM; 18.9 ± 1.4, $P < 0.01$). Hb levels at 24th hours of life were significantly higher in all groups compared to those in the control group (ICC; 16.5 ± 1.6 vs. DCC; 18.7 ± 2.2, CCM; 18.5 ± 2.0, ICM; 18.0 ± 2.0, $P < 0.05$), but were found to be similar among study groups.

Hematocrit (HTC) levels at birth were significantly higher in the ICM group compared to other groups (ICM; 55.2± 4.6 vs. ICC; 47.1± 4.8, DCC; 48.4 ± 6.9, CCM; 50.2 ± 6.4). Hematocrit levels were significantly higher in all groups at the 24th hour of life compared to those in the control group and were highest in the DCC and ICM groups (ICC; 45.7± 4.7 vs DCC; 52.6 ± 5.9, CCM; 51.8 ± 5.5, ICM; 52.4 ± 4.4, $P < 0.05$). There were no significant differences among DCC, CCM and ICM groups in terms of hematocrit levels at 24th hours of life.

The changes in Hb levels from birth to 24th hours of life (ΔHb) were statistically significant in DCC group ($P < 0.05$) (ICC; - 0.1± 1.5 vs DCC; 1.7 ± 2.6, CCM; 1.1 ± 2.5, ICM; - 0.9 ± 1.1). Hematocrit level changes from birth to 24th hours of life (ΔHct) were also statistically significant in DCC group ($P < 0.05$) (ICC; - 1 ± 4.4 vs DCC; 4.5 ± 7.3, CCM; 1.5 ± 6.3, ICM; - 2.9 ± 3.3). Hematological parameters at birth and 24th hours of life as well as the changes in hematological parameters are shown in Table 2.

None of the infants developed respiratory problems such as transient tachypnea of newborns or respiratory

Table 1. Demographical Characteristics of Neonates

Characteristics	ICC (N = 30)	DCC (N = 30)	CCM (N = 30)	ICM (N = 30)	P - Value
Gestational age (weeks)	(37 - 40)	(37 - 41)	(37 - 40)	(37 - 41)	> 0.05
Mean ± SD (range)	38.5 ± 1.0	38.7 ± 1.0	38.4 ± 1.0	38.3 ± 1.1	
Birth weight (g)	(2700 - 4850)	(2500 - 4475)	(2365 - 3800)	(2365 - 3800)	> 0.05
Mean ± SD	3420 ± 494	3260 ± 455	3200 ± 365	3170 ± 340	
Gender (n)	30	30	30	30	
Girl/boy	15/15	15/15	15/15	15/15	
Mode of delivery (n)	30	30	30	30	
Cesarean/vaginal delivery	15/15	15/15	15/15	15/15	
Need of resuscitation	None	None	None	None	

Table 2. Hematological Parameters at Birth and 24th Hours of Life [a, b, c]

Parameters	ICC (N = 30)	DCC (N = 30)	CCM (N = 30)	ICM (N = 30)
Hb at birth, g/dL	16.6 ± 1.9 (12.3 - 20.4)	16.8 ± 2.4(12.6 - 23)	17.5 ± 2.4 (14.3 - 22.8)	18.9 ± 1.4 (16.3 - 20.7)
Hb at 24th hour, g/dL	16.5 ± 1.6 (11.8 - 19.5)	18.7 ± 2.2 (13.9 - 22.6)	18.5 ± 2.0 (14.2 - 24.0)	18.0 ± 2.0 (16.0 - 21.4)
Hct at birth, %	47.1 ± 4.8 (37.5 - 58.9)	48.4 ± 6.9(34.3 - 66.1)	50.2 ± 6.4 (42.0 - 64.7)	55.2 ± 4.6 (46.9 - 61.3)
Hct at 24th hour, %	45.7 ± 4.7 (33.4 - 56.1)	52.6 ± 5.9 (37.7 - 63.9)	51.8 ± 5.5 (41.5 - 65.6)	52.4 ± 4.4 (47.1 - 61.6)
ΔHb, **g/dL**	- 0.1 ± 1.5 (- 2.8 - 3.3)	1.7 ± 2.6 (- 2.7 - 8.2)	1.1 ± 2.5 (- 3.8 - 4.5)	- 0.9 ± 1.1 (- 3.2 - 1)
ΔHct, **g/dL**	- 1.3 ± 4.4 (- 8.9 - 8.7)	4.5 ± 7.3 (- 8.1 - 28.3)	1.5 ± 6.3 (- 11.4 - 13.1)	- 2.9 ± 3.3 (- 8.6 - 3.4)

[a] One-way ANOVA, P < 0.01
[b] $\Delta HB = (Hb\,at\,24th\,hour)\ (Hb\,at\,birth)$
[c] $\Delta Hct = (HCT\,at\,24th\,hour)\ (HCT\,at\,birth)$

distress syndrome. Development of polycythemia and hyperbilirubinemia, as well as the necessary phototherapy rates, were similar in groups. Neonatal outcomes are detailed in Table 3.

5. Discussion

This study demonstrated that milking the umbilical cord significantly increased the volume of placental transfusion, such as deferred cord clamping. All study groups had higher hematological parameters at the 24th hour of life when compared to the control ICC group. Intact cord milking was associated with higher Hb and Hct levels at birth. The increases in the levels of both Hb and Hct from birth to the 24th hour of life was significantly higher in the DCC group. Short-term outcomes such as polycythemia, hyperbilirubinemia, necessary phototherapy, and respiratory problems were similar in all groups and were not influenced by placental transfusion technique differences.

It is argued that clear recommendations have not been presented concerning the optimum umbilical cord clamping time. Several randomized controlled trials have suggested delaying cord clamping with a duration of 30 - 60 seconds in order to maintain higher blood volume and achieve better oxygenation (5). World Health Organization (WHO) recommends that the umbilical cord should not be clamped earlier than one minute after birth (6). American Academy of Pediatrics (AAP) recommends a delay of at least 30 - 60 seconds for managing both term and preterm infants (7). Royal College of Obstetricians and Gynecologists (RCOG) and American College of Nurse-Midwives (ACNM) also suggest a delay of 2 - 5 minutes when dealing with both preterm and term infants (8, 9).

Umbilical cord milking maintains an increased placental transfusion during a shorter period (10 - 15 seconds). There are multiple systematic reviews about UCM in preterm infants showing increased blood pressure, hematological parameters, urinary output, cerebral oxygenation, and decreased risk of intraventricular hemorrhage, bronchopulmonary dysplasia, as well as necrotizing enterocolitis (3, 10, 11). A recent systematic review of 18 RCTs among 2834 preterm infants revealed that the DCC resulted in higher hematological parameters, reduced blood transfusion rates, and reduced hospital mortality (10). As for term infants, a Cochrane review evaluating 15 trials and 3911 infants showed that DCC led to higher hematological

Table 3. Neonatal Outcomes of Study Groups [a]

Groups	ICC (N = 30)	DCC (N = 30)	CCM (N = 30)	ICM (N = 30)
Respiratory problems	0	0	0	0
Polycythemia	0	1 (3.3)	1 (3.3)	1 (3.3)
Hyperbilirubinemia	7 (23.3)	4 (13.3)	4 (13.3)	8 (26)
Need of phototherapy	4 (13.3)	0	0	5 (16.6)

[a] Values are expressed as mean Na. (%).

parameters and reduced iron deficiency (12).

Transfer of placental blood to infant is associated with lower mortality and morbidities (13). The immediate clamping of the cord leads to approximately 20 to 40% of blood remaining in the placenta (14). American academy of pediatrics recommends delayed clamping in order to obtain the blood remaining in the placenta (7). ACOG and RCOG also recommends performing DCC at least 30 - 60 seconds after birth if the infant is a vigorous term or preterm infant (5, 8). In recent past, it was believed that waiting for DCC could harm the infants needing resuscitation, due to which UCM was adopted an alternative technique (15). Girish et al. (16) suggested the possibility of performing UCM on neonates requiring resuscitation.

Deferred cord clamping provides passive transfer of placental blood through slow pulsation of placenta, while UCM is an active method and is implemented faster (17). UCM can be implemented using an intact cord (ICM) or cut cord (CCM). In ICM technique, the blood is milked when the umbilical cord is still connected to the placenta, whereas CCM is performed after the umbilical cord is cut and separated from the placenta (13). It has been reported that ICM might increase pulmonary blood flow and assist lung expansion (5). McAdams et al. (18) demonstrated that ICM, compared to the CCM, had the potential to transfuse three to four times higher blood volume to newborns at birth, which was in agreement with our study result showing higher Hb and Hct levels at birth in the ICM group.

Several studies have shown the beneficial effects of DCC on hematological parameters and body iron stores, but limited trials have demonstrated the benefit of UCM for, especially, term neonates (15, 19). Studies have failed to reveal the harmful effects of UCM so far, and UCM has been reported to produce more favorable hematological parameters than ICC (14, 19). Colozzi (20) in the early 1950s reported that UCM produced 5-fold more favorable hematological parameters and higher blood pressure than ICC without producing any adverse effects. More recently, Upadhyay et al. (21) found higher Hb levels and iron status after performing cut-cord milking in a large randomized controlled trial including 200-term infants. Rabe et al. (22) also recorded more favorable hematological parameters for UCM. The higher hemoglobin levels reported by the latter may have been attributed to the implementation of the ICM technique compared to the CCM technique (20, 23). Hosono et al. (24) suggested that CCM may have produced more favorable hematological parameters. Another study found that performing CCM more than two times may have had no additional advantage since nearly 98% of the blood passed after conducting the milking procedure twice (18). Therefore, no clear recommendation was offered due to these findings. It was suggested that further studies should be carried out in order to clearly define the milking procedure of the umbilical cord in terms of the number of milking, speed of milking, and position of the infant. In this study, Hb and Hct levels at birth were significantly higher in ICM group compared to CCM; however, Hb and Hct levels at 24th hours of life were similar in these groups but were significantly higher than those in control ICC group.

A recent systematic review suggested that UCM may have been just as beneficial as DCC (25). All cited studies evaluating the hematological parameters documented higher results in the UCM group compared to ICC, and these results were compared with those in the DCC group (15, 21). Umbilical cord milking is a simple procedure that can be implemented easily and safely in few seconds. This method is less time-consuming, and could prove useful when dealing with infants in need of resuscitation (13). However, UCM as a standardized procedure has not been defined. Numerous studies have investigated different techniques, most of which have found larger placental transfusion in ICM.

5.1. Conclusions

To our knowledge, this study is one of the pioneering studies evaluating the effects of UCM techniques on short-term hematological parameters in term infants. Even ICM produced higher Hb and Hct levels at birth, and both milking methods (CCM and ICM) generated more favorable hematological parameters at 24th hour of life when compared to ICC, as was reported for DCC. As to the study limi-

tations, only short-term consequences of different placental transfusion strategies were examined by our study, and long-term data were not the subject of our study. It was suggested that both CCM and ICM may have been effective alternatives to DCC for sustaining placental transfusion.

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Footnotes

Authors' Contribution: B. Y. and M. C. conceptualized and designed the study. B. Y., I. G., E. D., A. B., and O. S. collected the data. B. Y., E. D. and M. C. analyzed and interpreted the data and conducted the literature search. B. Y. and M. C. drafted the article and wrote the manuscript. All authors contributed to the article and approved the submitted version.

Conflict of Interests: Authors declare that there is no funding support, no personal financial interests, no consultation fees, and no patents for this study. All authors also declare that they have no conflicts of interests. They all read and approved the final version of the article.

Data Reproducibility: The data presented in this study will be uploaded during the submission as research data file and will be openly available for readers upon request.

Ethical Approval: This study was approved by the local ethic committee of Kanuni Sultan Suleyman Training and Research Hospital under the ethical approval code of 2019.03.79. Ethical approval form can be reached using link: kanunieah.saglik.gov.tr/TR-672556/klinik-arastirmalar-etik-kurulu.html or sending direct e-mail to ethical committee secretariat at yesomozay@hotmail.com.

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