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Umbilical Cord Clamping Timing in Preterm Infants Delivered by Cesarean Section

*Manizheh Mostafa Gharehbaghi[1], Sanaz Yasrebinia[2], Parvin Mostafa Gharehbaghi[3]

[1]Professor of Pediatrics and Neonatology, Womens' Reproductive Health Research Center, Tabriz University of Medical Sciences, Tabriz, Iran.
[2]Neonatologist, Tabriz University of Medical Sciences, Tabriz, Iran.
[3]Professor of Obstetrics and Gynecology, Women's Reproductive Health Research Center, Tabriz University of Medical Sciences, Tabriz, Iran.

Abstract

Background: The timing of umbilical cord clamping may affect the need to blood transfusion and other morbidities of preterm infants. This study aimed to compare three different cord clamping timing (immediate cord clamping, delayed cord clamping and umbilical cord milking) in preterm infants delivered by cesarean section (CS).

Materials and Methods

A controlled randomized clinical trial was done in preterm infants with gestation age less than 32 weeks delivered by CS in AlZahra hospital, Tabriz, Iran from June 2018 up to the end of January 2019. They were randomly allocated in three groups consisted of 30 neonates in each group. Umbilical cord was clamped within 10 seconds after infant delivery in immediate cord clamping (ICC) group, 60 seconds after delivery in delayed cord clamping (DCC) group. Cord was milked toward the infant three times over two seconds duration in umbilical cord milking (UCM) group. All patients were followed until discharge for needing the blood transfusion, bronchopulmonary dysplasia and mortality.

Results: A total of 20 neonates of 90 studied neonates needed blood transfusion during hospital stay, of which, 4 neonates (13.3%) were in UCM group, 7 neonates (23.3%) in DCC group and 9 patients (30%) in ICC group (P= 0.27). The mean hemoglobin was significantly higher in UCM group at admission and 30 days after birth (P<0.05).

Conclusion

UCM may be as effective as DCC to increase hemoglobin in preterm infants delivered by CS. Although the hemoglobin of infants with DCC and UCM was significantly higher than infants with ICC, the rate of blood transfusion was not significantly decreased during hospital stay.

Key Words: Blood transfusion, Cesarean section, Preterm infants, Umbilical cord clamping.

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Corresponding Author:

Manizheh Mostafa Gharehbaghi, Professor of Pediatrics and Neonatology, Women's Reproductive Health Research Center, Tabriz University of Medical Sciences, Tabriz, Iran.

Email: gharehbaghimm@yahoo.com

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1- INTRODUCTION

The timing of cord clamping after birth may affect the amount of blood transfused from placenta to the neonate. Uterine contractions increase blood volume about 5-15 cc/kg during the first 5-15 seconds after delivery (1). The immediate cord clamping is routine practice in preterm infants because of anxiety about the risks of delayed resuscitation, hyperbilirubinemia or polycythemia with delayed cord clamping. Delayed cord clamping may provide up to 30% more blood volume and 60% more red blood cells to neonate in comparison to immediate cord clamping (2).

The American College of Obstetrics and Gynecologists recommends delayed cord clamping (DCC) for preterm and full- term newborns (3). There is increasing evidence which suggests delayed umbilical cord clamping may be beneficial. Delayed cord clamping may be beneficial because of the increased amount of placental blood received by neonate and improved transit from fetal to neonatal life (4-6). Improved blood pressure, reduced need for blood transfusion, intra-ventricular hemorrhage, necrotizing enterocolitis and infection are shown by delayed umbilical cord clamping in infants born before 37 weeks of gestation (5, 7).

Umbilical cord milking is an alternative to delayed cord clamping in which unclamped umbilical cord is grasped and blood is pushed toward the infant within 20 seconds before it is clamped. Some studies demonstrated that infants delivered at less than 33 weeks who undergo umbilical cord milking have higher hemoglobin and are at lower risk for bronchopulmonary dysplasia and intra-ventricular hemorrhage in comparison with immediate cord clamping (8). Some studies have compared delayed umbilical cord clamping with cord milking in preterm infants with different results. It is shown that delayed cord clamping may be not be beneficial for infants delivered by cesarean section (9-11). The systematic review of 18 randomized clinical trials (RCTs) of delayed versus early clamping consisting of 2,834 infants born <37 weeks' gestation (12) showed DCC is well tolerated by neonates with no adverse effect on Apgar scores or temperature at admission. It is associated with reduced mortality before discharge, no significantly different rate of retinopathy of prematurity (ROP), necrotizing enterocolitis (NEC), bronchopulmonary dysplasia (BPD) or late onset sepsis that is in contrast to another systematic review of RCTs (5, 13). Subgroup analysis of infants born by cesarean section vs. vaginal delivery showed no difference for mortality or above-mentioned morbidity. It is suggested that umbilical cord milking may be more efficient in preterm infants delivered by cesarean section (14). Since most preterm infants are born by cesarean section, we conducted this study to compare the efficacy of three different timing methods (immediate cord clamping, delayed cord clamping and umbilical cord milking) of cord clamping in preterm infants born at or less than 32 weeks gestation age.

2- MATERIALS AND METHODS

2-1. Study design and population

The randomized controlled clinical trial was conducted at a single referral tertiary university hospital (Al-Zahra hospital) in North-West of Iran from June 2018 up to end of January 2019. Pregnant women at less than 32 weeks' gestation admitted for cesarean section were enrolled in the study. Sample sizes were calculated based on previous randomized study of cord milking (15). With a Significance level (Alpha level) of 0.05 and beta level of 0.80, at least 25 infants in each group would be required to demonstrate a 10% difference in hemoglobin.

2-2. Exclusion criteria

Patients with placental abruption, placenta previa, known Rh sensitization, hydrops fetalis, mono chorionic multiples, nuchal cords and infants with major anomalies or who need immediate resuscitation were excluded from the study.

2-3. Methods

Computer generated random numbers in opaque sealed envelopes just before delivery randomly assigned the patients to three groups (immediate cord clamping, delayed cord clamping and umbilical cord milking). A clock in the operation room was used for timing. The primary outcome was anemia of prematurity and need of blood transfusion; and the secondary outcome was the bronchopulmonary dysplasia (BPD), and duration of hospital stay.

2-4. Intervention

In delayed cord clamping (DCC) group, 60 seconds elapsed from when the infant was delivered until the obstetrician assistant clamped the time the umbilical cord. The infant was held at the same level as the placenta in umbilical cord milking (UCM) group. By holding the placental end of umbilical cord, gently milked blood within umbilical vessels was directed toward the neonate over 2 seconds duration three times with a brief pause between each milking motion. Cord clamping was performed within 10 seconds after infant delivery in immediate cord clamping (ICC) group. Our Center's policy is resuscitation according to Neonatal Resuscitation Program (NRP) (18), and stabilization of infant by using CPAP for preterm neonates in delivery room and saving intubation only for those who have apnea or ineffective respiration. There was not any data about cord clamping time in neonatal chart for neonatologist managing the neonates.

2-5. Laboratory measurements

The hemoglobin and hematocrit level was measured by venipuncture at 6 hours after birth, one month of age and at discharge in all neonates. We considered hematocrit above 65% as polycythemia (16)**.** Cranial ultrasound examination was performed on days 5 to 7 of birth for the diagnosis of intraventricular hemorrhage (IVH) by an experienced pediatric radiologist. BPD was defined as the need for supplemental oxygen for at least 28 days and its severity was determined at 36 weeks of gestation age based on the fraction of inspired oxygen (17). Patent ductus arteriosus (PDA) was diagnosed based on clinical signs and confirmed by echocardiography performed by an expert pediatric cardiologist. Infants with moderate to severe cardiac or respiratory diseases received blood transfusion to maintain hematocrit 30-40%. An experienced nurse who was not aware about the studies' objective and patient's groups recorded all data.

2-6. Ethical consideration

Ethic committee of Tabriz University of Medical Sciences approved the study and it was registered in Iranian Registry of Clinical Trials (IRCT) by number IRCT 201702063915N. Written informed consent was obtained from parents.

2-7. Data Analyses

A person who was not involved in the diagnosis and treatment of infants using SPSS software version16.0 performed the analyses. Quantitative data were presented as mean ±standard deviation (SD) and qualitative data as frequency and percentage. Categorical data were analyzed by Chi-square test or Fisher's exact test. Normally distributed quantitative variables were compared by student's t-test. One way ANOVA was used for continuous outcomes. A p-value

of less than 0.05 was considered statistically significant.

3- RESULTS

A total of 90 patients with gestation age 32 weeks or less delivered by cesarean section that met inclusion criteria were enrolled in this study. Each group (immediate cord clamping, delayed cord clamping and umbilical cord milking) consisted of 30 neonates. The mean gestation age of studied infants was 30.6±1.37 weeks and their birth weight was 1176±138 grams, fifty-five neonates (56.6%) were girls. The most common maternal risk factor was preeclampsia in 31 (34.4%) cases, followed by hypothyroidism in 13 (14.4%), and diabetes mellitus in four (4.4%) patients. The infants in three groups were similar with respect to baseline characteristics that are shown in **Table.1**.

Table-1: Baseline characteristics of patients in three groups (n=90).

Variables	ICC group n=30	DCC group n=30	UCM group n=30	P- value
Gestation age, wk	30.80±1.56	30.80±1.06	30.46±1.45	0.55
Birth weight, gr	1214±43	1150±134	1165±191	0.18
Male, n (%)	21(70)	13 (43.3)	17 (56.6)	0.11
Apgar score				
1min	7.70±1.2	6.36±1.4	7.51±1.0	0.001
5 min	9.03±1.0	8.46±0.7	8.72±0.8	0.06
Antenatal corticosteroids				0.15
No	4	2	2	
1 dose	7	6	11	
2 doses	19	22	17	

ICC=immediate cord clamping, DCC= delayed cord clamping, UCM=umbilical cord milking.

In the UCM group 4 neonates (13.3%) needed packed cell transfusion during hospital stay compared with 7 neonates (23.3%) in DCC group and 9 patients (30%) in ICC group, p= 0.27. The hemoglobin and hematocrit concentrations at different ages are shown in **Table.2**.

Table-2: Laboratory and clinical measurements in studied patients (n=90).

Variables	ICC group n=30	DCC group n=30	UCM group n=30	P- value
Hb at admission, g/dl	18.29±2.0	18.66±1.8	19.69±2.3	0.03
Hb at 1 month, g/dl	13.68±2.8	13.51±3.1	14.32±3.9	0.003
Hb at discharge, g/dl	11.38±1.9	12.38±2.4	14.74±3.2	0.64
TSB at day 7, mg/dl	8.8±1.4	9.01±2.0	9.52±1.9	0.05
Need for mechanical ventilation, n (%)	7 (23.3)	6 (20)	2(6.6)	0.19
Duration of O_2 therapy, d	14.41±12.8	13.03±8.5	12.5±14.0	0.82
Surfactant therapy, n (%)	20 (66)	17(56)	22 (73)	0.56
PDA, n (%)	2(6.6)	4(13.3)	6(20)	0.32

ICC= immediate cord clamping, DCC= delayed cord clamping, UCM= umbilical cord milking, Hb= hemoglobin, TSB= total serum bilirubin, PDA= patent ductus arteriosus.

Phototherapy was needed for 21 neonates in ICC group, 26 cases in DCC group and all patients in UCM group (p=0.002). Duration of hospital stay was 26.23±16.6 days in ICC group, 27.3±14.13 days in DCC group and 22.46±14.6 days in UCM

group (p=0.43). IVH was diagnosed in 10 neonates (11.1%), six cases were in DCC group (five neonates had IVH grade I and one case grade II). Four neonates in UCM group developed IVH, two cases were grade I and two cases grade II, P=0.13. BPD was defined in six patients in ICC group, four neonates in DCC group and two neonates in UCM (p=0.31). No infant had polycytemia or need of exchange transfusion for management of hyperbilirubinemia.

4- DISCUSSION

This study aimed to determine the optimum method for umbilical cord clamping in preterm infants delivered by cesarean section. In our study, UCM was as effective as DCC with respect to blood transfusion, PDA, IVH and BPD. The hemoglobin and hematocrit was higher in patients with delayed cord clamping and umbilical cord milking in our study. The need for blood transfusion was diminished in patients with umbilical cord milking during their hospital stay but the difference was not statistically significant. All cases of transfusion were after the first 4 weeks of birth. These infants had higher total serum bilirubin and significantly higher rate of phototherapy. In the study of March and co-workers (1), the neonates in UCM group had a significantly lower rate of blood transfusion before 14 days of life in comparison with neonates in ICC group.

Similar to our study, at the first 28 days of life the rate of blood transfusion was not different between groups. The need of transfusion depends on many factors including the severity of oxygen dependency. It is suggested that infants with UCM have higher blood pressure and are more stable in the first weeks of life. March et al. reported lower rate of IVH with UCM than ICC but the grade III and IV of IVH was similar in these groups (1). The rate of IVH was not significantly decreased in patients with DCC in our study. Tarnow-Mordi et al. (19) reported results of the Australian placental transfusion study, in which 1,566 infants born before 30 weeks of gestation were randomly assigned to immediate cord clamping or at 60 seconds. There was no significant difference between the two groups in the primary outcome of death or major morbidity by 36 weeks of post-menstrual age in their study. One limitation with DCC is required delay of 30 seconds or more in neonatal resuscitation during delivery. In a systematic review, DCC reduced the rate of Apgar score less than 4 at 1 minute with marginal statistical significance without increase in the proportion of infants with Apgar score less than 8 at 5 minutes (12).

Although the mean Apgar score was lower in DCC group in our study, the median Apgar score was not less than five. The meta-analyses carried out so far have shown no differences between delayed cord clamping and early cord clamping groups in terms of Apgar scores and body temperatures taken on admission to the newborn unit (20). Colm et al. (21) suggested need to provide breathing support to babies in close proximity to their mothers, while they remained attached to the placenta. They recommended future studies with focus on clamping relative to the onset of breathing or ventilation, rather than the number of seconds after birth. Aladangady et al. (9) reported lower blood volume in neonates who were born by cesarean section and DCC compared with infants who were delivered vaginally. It is suggested more blood remains in placenta with cesarean section because of impaired uterine contractions by anesthetics and surgical interventions. In another study, DCC performed with the infant held at increasingly lower level below introitus or incision results in increasing reduction in blood transfusion irrespective of mode of delivery (22). There is a concern about the

risk of hyperbilirubinemia with delayed cord clamping. The mean bilirubin concentration was higher in DCC group in present study, but exchange transfusion was not indicated in any neonates. In contrast to our study, the need for phototherapy was not increased significantly in March et al.'s study, despite higher hemoglobin and hematocrit in UCM group in their study (1). DCC may increase red blood cell mass parallel with increase in number and concentration of mesenchymal stem cells (22). It may enhance the modulation of excessive inflammatory reactions. In our study, the occurrence of BPD was not significantly different between groups. So, future studies are recommended with assessment of inflammatory reactions.

4-1. Study Limitations

The main limitation of our study was the small number of studied patients and lack of their long-term follow- up. We do not have video records of deliveries, and have not assessed the cord clamping time in relation with infant breathing.

5- CONCLUSION

In conclusion, although the optimal time of umbilical cord clamping for premature infants is still controversial, delayed cord clamping is accepted as reliable. UCM may be as effective as DCC in increasing neonatal hemoglobin in preterm infants delivered by CS. The rate of blood transfusion in the first month of life was not significantly decreased by DCC or UCM. Future studies with a large number of patients and long-term follow-up routine umbilical cord milking is recommended.

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7- CONFLICT OF INTEREST: None.

8- REFERENCES

1. March MI, Hacker MR, Parson AW, Modest AM, de Vecino M. The effects of umbilical cord milking inextermely preterm infants: A randomized controlled trial. J Perinatol 2013; 33: 763-67.

2. Strauss RG, Moch DM, Johnson KJ, Cress GA, Burmeistewr LF, Zimneman MB, et al. A randomized clinical trial comparing immediate versus delayed claming of umbilical cord in preterm infants: short term clinical and laboratory endpoints.Transfusion 2008; 48: 658-65.

3. Committee on Obstetric practice committee opinion No. 684: delayed umbilical cord clamping after birth. ObstetGynecol 2017; 129:e5-10.

4. Moradi WT, Morris J, Kiby A, Robledo K, Askie L, Brown R, et al. delayed cord clamping in preterm infants. The New Engl J Med. 2012; 377:2445-55.

5. Rabe H, Reynolds G, Diaz-Rossello JL. A systematic review and meta-analysis of a brief delay in clamping of umbilical cord of preterm infants. Neonatology 2008; 93:138-44.

6. Manley BJ, Owen LS, Hooper SB, Jacobs SE, Cheong JLY, Doyle LW, et al. Towards evidence based resuscitation of newborn infants. Lancet 2017; 389: 1639-48.

7. Robe H, Reynolds G, Draz- Rossello J. A systematic review and meta-analysis of a brief delay in clamping the umbilical cord of preterm infants. Neonatology 2008;93: 138-44.

8. Al-Wassian H, Shah PS. Efficacy and safety of cord milking at birth: a systematic review and meta- analysis. JAMA Pediatr 2015; 169 (1):18-25.

9. Aladangady N, Mc Hugh S, Aitchinsov TC, Wardrop CA, Holland BM. Infants blood

10. Struss RG, Mock DM, Johnson K, Mock NI, Cress G, Knosp L, et al. circulating RBC volume measured with biotinylated RBCs is

superior to the hematocrit to document the hematologic effect of delayed versus immediate umbilical cord clamping in preterm neonates. Transfusion 2003: 43 (8): 1168-72.

11. McDonnel M, Henderson-Smat DJ.Delayed umbilical cord clamping in preterm infants: A feasibility study. J Pediatr Child Health 1997; 33 (4): 308-10.

12. Fogarty M, Osborn DA, Askie L, Seider AL, Hunter K, Lui K, et al. delayed vs early umbilical cord clamping for preterm infants: a systematic review and meta-analysis. Am J Obstet Gynecol 2018. Doi 10.1016/j.ajog. 2017.10.231.

13. Rabe H, Diaz- Rosello JL, Duley L, Dowsewell T. Effect of timing umbilical cord clamping and other strategies to influence placental transfusion at preterm birth on maternal and infant outcomes. Cochrane Database Syst Rev 2012; 15 (8): CD003248. doi: 10.1002/14651858.CD003248.pub3.

14. Katheria AC, Truong G, Cousins L, Oshiro B, Finer NN.Umbilical cord versus delayed cord clamping in preterm infants. Pediatrics 2015; 136 (1): 61-9.

15. kumar B, Upadhyay A, Gothwal S, Jaiswal V, Joshi P, Dubey K. Umbilical cord milking and hematological parameters in moderate to late preterm neonates: a randomized controlled trial. IndianPediatr 2015; 52: 753-57.

16. Alsafadi TRM, Hashmi SM, Youssef HA, SulimanAK, Mansour Abbas H, Albaloushi MH. J Clin Neonatol. 2014; 3 (2): 93–8.

17. Jobe AH, Bancalari E. Bronchopulmonary dysplasia. Am J Resp Crit Care. 2001. 163: 1723-29.

18- Weiner G M, Zaichkin J, American Academy of Pediatrics and American Heart Association. Textbook of Neonatal Resuscitation (NRP), 7th Ed. 2016.

19. Tarnow-Mordi W, Morris J, Kirby A, et al. Delayed versus immediate cord clamping in preterm infants. N Engl J Med 2017; 377: 2445-55.

20. Gokalp AS, Gunlemez A, Oguz D. Umbilical Cord Clamping Time in Premature Infants. J Neonatal Biol 2017, 6:1.DOI:10.4172/2167-0897.1000248

21. Colm P.F. O'Donnell, M.B., B.Ch. The Timing of Cord Clamping for Preterm Infants N Engl J Med. 2017; 377; 25 :2488-89.

22. Prockop DJ, Oh JY. Mesenchymal stem/stromal cells: roles as guardians of inflammation. Mol Ther 2012; 20: 14-20.