



ARAŞTIRMA / RESEARCH

Effect of delayed cord clamping on short term clinical and laboratory findings in term and late preterm infants

Geciktirilmiş kord klemlemenin term ve geç preterm bebeklerin kısa dönem klinik ve laboratuvar bulgularına etkisi

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Abstract

Purpose: Delaying the cord clamping for at least 30 seconds in infants who did not require cardiopulmonary resuscitation after birth has been recommended in the revised guidelines of American Academy of Pediatrics in 2015. We aimed to evaluate the effect of delayed cord clamping on hematological and biochemical parameters, need for hospitalization, oxygen, mechanical ventilation, phototherapy, and on sepsis, hyperbilirubinemia rate in late preterm and term infants.

Material and Methods: This prospective study included 86 infants with a gestational age of 34 to 41 weeks. Infants were randomly included in one of two groups. While cords of 43 infants were clamped immediately after birth, cords of the other 43 infants were clamped after one minute. Hematological and biochemical values were evaluated both in cord blood and venous blood samples on 7th day of life.

Results: Hemoglobin and hematocrit values were similar in two groups both in cord blood and on 7th day of life. Delayed cord clamping resulted in statistically significant decrease in the leukocyte and platelet count and creatinine levels in the cord blood. Mechanical ventilation requirement was significantly lower in the delayed cord clamping group. Hospitalization rate, sepsis rate and hyperbilirubinemia rate were similar in both groups.

Conclusion: Delayed cord clamping caused lower leukocyte, platelet counts and lower creatinine levels in cord blood. There seems a beneficial effect on respiratory status in late preterm and term infants.

Keywords: : Infants, cord clamping time, hospitalization, sepsis, mechanical ventilation

Öz

Amaç: Amerikan Pediatri Akademisi tarafından 2015 protokollerinde doğumdan sonra canlandırma ihtiyacı olmayan bebeklerde kord klemlemenin en az 30 dk geciktirilmesi önerilmiştir. Bu çalışmada term ve geç preterm bebeklerde geciktirilmiş kord klemlemenin, hematolojik ve biyokimyasal parametreler, hastaneye yatış, oksijen, mekanik ventilasyon, fototerapi ihtiyacına ve sepsis, hiperbilirubinemi hızına etkisini değerlendirmeyi amaçladık.

Yöntem: Prospektif çalışmamıza 34-41 gebelik haftasındaki 86 bebek dahil edildi. Bebekler randomize olarak iki gruba ayrıldı. 43 bebeğin göbek kordonu doğumdan hemen sonra klemplenirken diğer 43 bebeğin kordonu doğumdan 1 dakika sonra klemplendi. Hematolojik ve biyokimyasal parametreler hem kord kanında hem de postnatal 7. günde alınan venöz örneklerde değerlendirildi.

Bulgular: Hemoglobin ve hematokrit değerleri hem kord kanında hem de postnatal 7. günde her iki grupta da benzerdi. Geciktirilmiş kord klemplenme grupta kord kanında lökosit ve trombosit değerleri istatistiksel olarak anlamlı düşüktü. Geciktirilmiş kord klemplenme grupta kord kanında kreatinin düzeyi anlamlı olarak düşük saptandı. Mekanik ventilasyon ihtiyacı kord klemplenme grupta daha azdı. Hastaneye yatış, sepsis ve hiperbilirubinemi hızı her iki grupta da benzerdi.

Sonuç: Geciktirilmiş kord klemlemenin term ve geç preterm bebeklerde lökosit, trombosit ve kreatinin düzeylerinde düşüklüğe neden olduğu, solunum üzerine olumlu etkileri olduğu düşünüldü.

Anahtar kelimeler: Yenidoğan, kord klemleme zamanı, kreatinin, lökosit sayısı, mekanik ventilasyon

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INTRODUCTION

For many years, various recommendations were made regarding the cord clamping time after birth. Especially, in the recent years, studies have presented that delaying cord clamping would have beneficial contributions to the health of the infant, and would not have any undesirable effect on both mother and the newborn¹.

Placenta contains approximately 75-125 cc of blood. One quarter of this blood is transferred from placenta to infant within the first 15 second, and a half within a minute. Delayed cord clamping (DCC) increases the amount of blood by approximately 30% in infants. Thus increase in hematocrite level and total bilirubin level can be expected. A study has found that the amount of blood in term infants was 99 cc/kg in the group with delayed cord clamping and 78 cc/kg in the group with early cord clamping. The same study also found that while hematocrit value at birth was similar in both groups, the hematocrit value at hour 48 was 48% in the group with early clamping and 65% in the group with delayed clamping²⁻⁵.

Delaying the cord clamping for at least 30 seconds in infants who did not require cardiopulmonary resuscitation has been recommended in the revised guidelines of American Academy of Pediatrics in 2015. While this application does not have any adverse effects on survival, it has beneficial effects including higher blood pressure, less necrotizing enterocolitis, rarer and lower grade of intraventricular hemorrhage, and less postpartum blood transfusion need⁶. The recent evidence has recommended for the use of DCC by many professional organizations in the fields of obstetrics, midwifery, and pediatrics. However, despite these recommendations, widespread adoption of these policies has been difficult.

We hypothesized that DCC may increase hematocrite levels, decrease ventilator support and oxygen requirement by improving intravascular volume and tissue oxygenation, lower intraventricular hemorrhage and sepsis. In this prospective study, we aimed to evaluate if delaying umbilical cord clamping had any effect on hematological and biochemical parameters, need for hospitalization, oxygen, mechanical ventilation and phototherapy, and on sepsis and hyperbilirubinemia rate in late preterm and term infants in newborn period.

MATERIALS AND METHOD

The study included infants who were born with gestational age over 34 weeks between February 2017 and March 2017 in Gynecology and Obstetrics Department of Çukurova University. The study was approved by Çukurova University, Faculty of Medicine, Non-Interventional Clinical Research Ethics Committee (October 7, 2016-Decision No:16) and the inform consent were taken of all participating infants' parents.

Procedure

Infants of mothers with diabetes mellitus using insulin, infants of mothers with ablatio placenta, abruptio placenta, twin infants with single placenta, infants with anomalies incompatible with life, infants who were born in other center and transported to unit, infants with severe intrauterine growth retardation, and pregnancies with suspicion of twin-to-twin transfusion syndrome were excluded in the study. Infants were randomly grouped as delayed cord clamping group or immediate cord clamping group. Randomization was done digitally.

In immediate cord clamping group, cord was clamped just after the birth, while in delayed cord clamping group, cord was clamped one minute after birth. Infant was kept at the level or 30 cm below the uterus. Two milliliters of blood sample was taken from the cord blood, and peripheral vein on postpartum day 7. In these blood samples, complete blood count, total bilirubin, direct bilirubin, blood urea nitrogen (BUN), creatinine, total protein, albumin and ferritin levels were studied. Complete blood count was studied using light scattering method and XN1000 system (Sysmex, China), ferritin using chemiluminescence method and DXI800 system (Beckman Coulter, USA), total bilirubin, direct bilirubin, albumin, total protein, BUN and creatinine were measured using colorimetric method and DXC800 system (Beckman Coulter, USA).

All infant were observed for clinical and laboratory outcomes in the newborn period. If infants were not hospitalized or discharged before 7 days of life, they were examined on 7th day of life and then 28th day of life in the outpatient clinic. Prenatal characteristics including gestational week, multiple pregnancy and gender of the infant; natal characteristics including delivery route, birth weight, need for surfactant administration, and Apgar scores; and postnatal characteristics including need for resuscitation, sepsis

rate, hyperbilirubinemia requiring phototherapy, and need for transfusion, oxygen, exchange transfusion, invasive or non-invasive mechanical ventilation were evaluated for all infants. Patients were hospitalized due to either urinary infection of mother, respiratory distress or inability for effective sucking in postnatal 0-24 hours of life. Oxygen therapy was planned due to respiratory requirement and saturation of patients. Infants had mechanical ventilation when there was a resistant hypoxia or tachypnea.

The patients' need for phototherapy was determined according to the Guidelines for Neonatal Jaundices-2014 of Turkish Association of Neonatology⁷. Patients' sepsis assessment was evaluated to the Guidelines for Newborn Infections-2014 of Turkish Association of Neonatology⁸.

Statistical analysis

SPSS 20.0 package software was used for the statistical analysis of data. Categorical parameters

were summarized as number and percentage, and numerical parameters as mean and standard deviation (and minimum-maximum, if necessary). Chi-square test was used for the comparison of the categorical parameters between the groups. Mann Whitney U test was used for the comparison of non-normally distributed numerical parameters between two groups. Statistical significance level was taken as 0.05 in all tests.

RESULTS

Totally 86 infants were included in the study. Characteristics of the infant are shown in Table 1. There were no statistically significant differences between the gestational weeks, birth weights, delivery routes, gender and 5 minutes Apgar scores of the groups. However, first minute Apgar scores of the infants in delayed cord clamping group was lower ($p=0.04$). But none of the infants needed resuscitation in delivery room.

Table 1. Characteristics of the infants

	Immediate Cord Clamping Group n: 43	Delayed Cord Clamping Group n: 43	P
Gestational age* (week)	37.4±1.8 34-40	37.1±2.1 34-41	0.41
Birth Weight*(gram)	3094.4±656 1930-4750	3086.7±708 1600-4500	0.95
1. Min Apgar score*	8.09±0.64 6-9	7.6±1.25 3-9	0.04
5. Min Apgar score*	9.12±0.62 8-10	8.88±0.98 5-10	0.19
	n (%)	n (%)	
Male	18(41.9)	17(39.6)	0.66
C- section	35(81.3)	35(81.3)	1

*The values are shown as mean±SD, min-max.

No statistically significant differences were found between mean hemoglobin and hematocrit values in the cord blood and the 7th day blood sample of the infants ($p> 0.05$), (Table 2). Delayed cord clamping resulted in statistically significant decrease in the leukocyte and platelet count in the cord blood of infants (for leukocyte; 95% CI 14.0 to 16.7 in immediate cord clamping group and %95 CI 10.8 to 14.2 in delayed cord clamping group while for platelet; 95% CI 226.5 to 279.7 in immediate cord clamping group and %95 CI 179.3 to 239.9 in delayed cord clamping group, $p=0.01$, $p=0.032$, respectively). However, there was no statistically significant

difference in terms of leucocyte and platelet counts on day 7 ($p=0.94$, $p=0.80$) as shown in Table 2.

As shown in Table 3, no statistically significant differences were found between mean BUN, total protein, albumin, ferritin, total and direct bilirubin values in the cord blood and the 7th day blood sample ($p> 0.05$). Delayed cord clamping resulted in statistically significant decrease in the creatinine level in the cord blood sample of the infants (95%CI 0.59 to 0.71 in immediate cord clamping group and 95%CI 0.54 to 0.62 in delayed cord clamping group, $p=0.04$).

Table 2. Hematological values in the cord blood and venous blood on day 7

	Cord blood			Venous blood on day 7		
	Immediate Cord Clamping Group	Delayed Cord Clamping Group	p	Immediate Cord Clamping Group	Delayed Cord Clamping Group	p
Hemoglobin (g/dL)	17.5±2,3 13.1-21,3	17.08±3.2 7.5-23.5	0.45	16.9±2.4 13.2-22.7	16.9±3.09 7.8-21.7	0.99
Hematocrit (%)	51.7±6.4 39.1-63.1	50.7±9.4 51-69.6	0.57	48.9±6.6 38.2-62.7	49.7±7.9 31.2-63.5	0.61
Leukocyte count (10 ³ /μL)	15.3±4.3 7.9-25.8	12.4±5.5 3.6-27.3	0.01	12.3±2.8 7.4-18.1	12.3±3.7 7.3-26.1	0.94
Platelet (10 ³ /μL)	253.1±86.4 30-433	209.6±98.3 11-366	0.032	298.3±97.7 99-347	326.2±103.8 17.3-553	0.80

The values are shown as mean±SD. min-max.

Table 3. Biochemical values in the cord blood and venous blood on day 7

	Cord blood			Venous blood on day 7		
	Immediate clamping N: 43	Delayed clamping N: 43	p	Immediate clamping N: 43	Delayed clamping N: 43	p
BUN (mg/dL)	7.2±2 3.6-12	7.5±2.2 4-15.4	0.54	6.68±5.6 0.6-23.1	7.6±6.4 0.9-31	0.47
Creatinine mg/dL	0.65±0.19 0.27-1.2	0.58±0.13 0.39-0.94	0.04	0.44±0.16 0.2-0.92	0.44±0.14 0.2-0.78	0.92
Total protein (g/dL)	5.01±0.7 3.8-6.3	4.99±0.53 4.2-6.3	0.89	4.9±0.55 3.6-6.1	5.08±0.33 4.5-5.8	0.35
Albumin (g/dL)	3.08±0.33 2.5-3.8	3.15±0.4 2.7-4.2	0.34	3±0.4 2.2-4	3.1±0.37 2.3-4.4	0.15
Ferritin (ng/mL)	131.5±78.3 33.6-494.4	124.1±84.7 8.2-494.4	0.67	228.7±112.8 57.7-479.7	203.7±101.8 19-482	0.28
Total bilirubin (mg/dL)	3.05±1.53 0.67-7.5	2.84±1.74 0.3-7.5	0.55	8.2±4.1 1.2-16.5	8.73±3.88 0.95-16.4	0.41
Direct bilirubin (mg/dL)	0.5±0.3 0.2-1	0.4±0.2 0.2-1.3	0.68	0.45±0.22 0.21-1.2	0.4±0.15 0.18-0.8	0.21

The values are shown as Mean±SD, Min-Max.

The infants with immediate or delayed cord clamping were assessed for hospitalization rates, need for oxygen and mechanical ventilation, sepsis development rates, and need for phototherapy. In these groups assessment, no statistically significant difference was detected in the hospitalization rate, need for oxygen and phototherapy, and sepsis development rate ($p>0.05$). However, need for

mechanical ventilation was lower in the delayed cord clamping group compared to the immediate cord clamping group, ($p=0.007$), (Table 4). Eighteen infants were treated for clinical sepsis. None of the infants had blood transfusion, surfactant administration or exchange transfusion. All of the hospitalized infants were discharged and all infants were healthy on 28th day of life.

Table 4. Postnatal characteristics of infants

	Immediate Cord Clamping Group n: 43 (%)	Delayed Cord Clamping Group n: 43 (%)	P
Hospitalization	26 (60.5)	27 (62.8)	0.82
Need for oxygen	11 (25.6)	12 (27.9)	0.80
Need for mechanical ventilation	9 (20.9)	1 (2.3)	0.007
Sepsis development	8 (18.6)	10 (23.3)	0.59
Need for phototherapy	10 (23.3)	13 (30.2)	0.46

DISCUSSION

This study evaluated the effect of delayed cord clamping on laboratory and clinical parameters of late preterm and term newborns and found that delayed cord clamping caused lower leucocytes and platelets counts and lower creatinine levels in the cord blood; however this effect was not continuous and there was no significant difference on day 7. Also mechanical ventilation need was lower in delayed cord clamping group.

While there are many studies about delaying of cord clamping in the literature, there are considerable differences in some investigations. Delaying cord clamping provides extra time for the transportation of the placental blood to the infants. The amount of the transported blood varies based on the level the infant is kept and the duration of delaying the clamping⁹. Delaying duration varies from 30 seconds to the time at cessation of cord pulsation. World Health Organization specified the time of delaying the cord clamping as 1 to 3 minutes¹⁰. In their study in preterm infants in 2008, Rabe et al.¹¹ defined the delayed cord clamping duration as at least 30 seconds, and the amount of the blood circulating at 24 hour in this group was found to be higher compared to the group with immediate clamping. In the present study, we clamped the cord one minute after in the delayed cord clamping group.

Many studies comparing the effect of delayed cord clamping on hemoglobin and hematocrite levels have found that early period hematocrite and hemoglobin levels were higher^{1,12-16}. Oliveira Fde C et al.¹⁷ studied term infants in 2014 and have found similar hemoglobin and hematocrite values in the cord blood samples of the infants with immediate cord clamping and 60-second delayed clamping. Our study also did not find any significant difference between the hemoglobin and hematocrit values in the cord blood sample and in the 7th day blood sample of the infants in both groups. The discordance between results of the studies might be explained by cord clamping durations and blood sampling times.

In our study, leukocyte counts in the cord blood in the infants with delayed cord clamping were found to be lower. The only study evaluating the effect of placental transfusion on leukocytes in the literature reported decreased leukocyte count in preterm infants \leq 32 gestational weeks who underwent cord milking¹⁸. In that study, neutrophil count on days 1, 3 and 7 in the group who underwent cord milking

before clamping were found to be lower than the group with immediate clamping. However, in our study this decrease was not detected in the blood taken on day 7. In our study placental transfusion was performed using delayed cord clamping method instead of cord milking method.

Ertekin et al.¹⁹ found that DCC up to 90–120 s increased the hemoglobin, hematocrit levels of infants significantly at the second month, but not at birth. In the same study they found that, ferritin levels of both groups did not differ in cord blood samples. In our study, no statistically significant difference was detected between ferritin values in the cord blood and 7th day blood sample of the infants in groups.

Qian et al.²⁰ reported that, in preterm neonates of 30–33 weeks of gestation, DCC had resulted in improved ferritin levels at discharge in comparison to ECC, but this benefit did not sustain till 3 months of postmenstrual age and also DCC did not affect the ferritin level at 10 weeks of age in infants born between 34 and 36 weeks' gestation. In a study by Ceriani Cernadas JM et al.²¹, it has been found that ferritin levels studied on month 6 were higher in term infants with delayed cord clamping compared to the infants with immediate cord clamping. As ferritin level in the cord blood was not studied in that study, it was not possible to interpret those results with our results.

While some of the studies in premature infants showed that delaying cord clamping results a decrease in the incidence of late-onset sepsis, others did not detect such a result^{16,22-24}. In our study, no statistically significant difference was detected in sepsis incidence in late preterm and term infants with delayed and immediate cord clamping.

Our study adds to literature that DCC decreases the creatine level. This is the first literature studying the effect of DCC on creatinin and showed that there is a lower creatinin level in DCC group. The laboratory results of cord blood of infants reflect the levels of mother serum levels. Increased cord blood creatinin level would be better to correlate with levels after 24hour of life in infants in further studies containing more infants. The effect of delaying cord clamping on phototherapy requirement in infants is controversial^{1,12,16,25,26}. In our study, there was no difference between phototherapy need of the groups.

In the present study, while there were no statistical difference for gestational week, birth weight, delivery route, gender, 5-minute Apgar scores, and the

hospitalization rate, the need for mechanical ventilation was statistically significantly lower in infants with delayed cord clamping. First minute Apgar score was lower in delayed clamped group, despite to same initial steps of resuscitation intervention for one minute. Also none of the infants needed further resuscitation in our study. The results of the meta-analysis by McDonald SJ et al.¹² have shown that there is no difference between the term infants with immediate and delayed cord clamping for 5 minute Apgar score and hospitalization rate. The decreased need for mechanical ventilation in the infants with delayed cord clamping might be either due to the excess blood transported to the infant or better hemodynamic status or both.

In conclusion, in this study, delaying cord clamping time was not found to have any effect on cord and 7th day blood hemoglobin and hematocrit levels; however it caused lower leukocyte and platelet counts, and lower creatinine levels in cord blood. Hospitalization rate, sepsis and phototherapy rate did not differ but mechanical ventilation rate was lower in delayed cord clamping group. We suggest further studies with larger series to evaluate the effect of delayed cord clamping on laboratory and clinical outcomes.

Yazar Katkıları: Çalışma konsepti/Tasarımı: MS, NB; Veri toplama: NB, HS, SB; Veri analizi ve yorumlama: MS, MH, FÖ; Yazı taslağı: MS, NB; İçeriğin eleştirel incelenmesi: MS, HYY, FÖ; Son onay ve sorumluluk: MS, NB, HŞ, HYY, FÖ, SB; Teknik ve malzeme desteği: NB, HŞ, SB; Süpervizyon: MS, HY, FÖ; Fon sağlama (mevcut ise): yok.
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