

Relationship Between Umbilical Cord Milking and Development of Retinopathy of Prematurity

Umbilikal Kordon Sağlamasıyla Prematüre Retinopatisi Gelişimi Arasındaki İlişki

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ABSTRACT

Purpose: This study aimed to investigate the relationship between umbilical cord milking (UCM) and development of retinopathy of prematurity (ROP).

Methods: We included neonates (n =75) who were screened for ROP at a neonatal intensive care unit between October 2015 and April 2016 with a gestational age of <32 weeks and follow-up of 43 weeks post-delivery. The findings were classified according to the International Classification of Retinopathy of Prematurity. We classified infants into 2 subgroups: group A included patients who underwent UCM (n=38); group B included patients who did not undergo UCM (n=37), and the umbilical cord was clamped immediately after birth. A retrospective review of records was performed and statistical analyses were evaluated.

Results: Four patients in group A and 4 in group B were diagnosed with mild ROP disease, which then spontaneously regressed. One patient in group A and 2 patients in group B were diagnosed with stage 3 ROP and received laser photocoagulation treatment. None of the neonates were affected by more severe stages of ROP or required further surgical interventions. Analysis by chi-square test showed no significant difference in development of ROP between the 2 groups (P=0.763).

Conclusions: To our knowledge, this is the first study to focus on the effect of UCM on development of ROP. Although we did not find any significant correlation, more neonates were required laser treatment in non-UCM group.

Key words: Retinopathy of prematurity, umbilical cord milking, premature birth.

ÖZ

Amaç: Bu çalışmada umbilikal kordon sağması ile premature retinopatisi gelişimi arasındaki ilişki incelenmiştir.

Metod: Çalışmaya Ekim 2015 ile Nisan 2016 arasında yenidoğan yoğun bakım ünitesinde premature retinopatisi nedeniyle doğum sonrası 43. haftaya kadar takip edilmiş <32 doğum haftalı bebekler dahil edilmiştir. Bulgular Uluslararası Premature Retinopatisi Sınıflamasına göre sınıflandırılmıştır. Yenidoğanları iki gruba ayırdık; A grubu umbilikal kordon sağması yapılanlar (n=38), B grubu ise sağma yapılmadan doğum sonrası kordonu hemen klemlenenlerdir (n=37). Dosyalar geriye dönük olarak taranmış ve bulgular istatistiksel analiz eşliğinde değerlendirilmiştir.

Bulgular: A ve B grubunda dörder hasta da tedavi gerektirmeyen retinopati gelişti ve takiplerde regrese oldu. A grubunda 1 hastada, B grubunda ise 2 hastada ever 3 prematüre retinopatisi gelişti ve laser fotokoagülasyon uygulandı. Yenidoğanların hiçbirinde daha ciddi retinopati gelişmedi ve cerrahi girişim gerekmedi. Ki-kare testi analizine göre premature retinopatisi gelişimi açısından iki grup arasında fark bulunamadı. (p=0.763)

Sonuç: Bilindiği kadarıyla bu çalışma, umbilikal kordon sağmasının premature retinopatisi gelişimine etkisini araştıran ilk çalışma. Anlamlı bir etki bulunamamasına rağmen sağma yapılmayan grupta daha fazla hastaya laser tedavisi gerekmiştir.

Anahtar Kelimeler: premature retinopatisi, umbilikal kordon sağması, prematüre doğum.

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INTRODUCTION

Retinopathy of prematurity (ROP) is a major cause of avoidable blindness in preterm infants in developed and developing countries.¹ Approximately 50,000 children suffer from visual impairment secondary to ROP worldwide.²

Prematurity, low birth weight, respiratory distress syndrome, and prolonged oxygen treatment increase the risk of ROP development.³ Additionally, blood transfusion and mechanical ventilation are independent risk factors for predicting development of ROP disease.^{4,7}

Weintraub et al. reported that the incidence of stage 3 ROP was increased 14-fold in neonates who received blood transfusions.⁷ They also showed that a reduction in blood transfusions led to a reduction in the incidence of severe ROP. Dani et al. suggested that limiting the amount of blood provided to preterm infants could contribute to reducing the incidence of ROP.⁸ Another study demonstrated that a decreased erythrocyte transfusion rate lowered the incidence of ROP.⁴

Previous studies have shown that early cord clamping can deprive the neonate of approximately a quarter of its blood volume.⁹ Umbilical cord milking (UCM) is a cost free, safe procedure that is performed in the delivery room within 20 seconds by grasping the unclamped umbilical cord and pushing the blood towards the neonate.¹⁰ Previous studies have shown that UCM appears to improve systemic blood flow and perfusion.¹¹ UCM also leads to higher serum hemoglobin levels, fewer blood transfusions, fewer days on oxygen therapy, and less frequent use of oxygen.¹¹⁻¹³

Therefore, based on previous reports, we hypothesized that UCM reduces the incidence of ROP in preterm infants by reducing the need for blood transfusions and respiratory support in very preterm infants.

MATERIALS AND METHODS

This study was approved by the local Institutional Review Board and Ethics Committee. In this retrospective study, 75 infants at gestational age ≤ 32 weeks, who were born between October 2015 and April 2016, were enrolled. The subjects were divided into 2 groups: those who underwent UCM (group A, UCM group, $n = 38$) and those who did not, with the umbilical cord clamped immediately after birth (group B, control group, $n = 37$). In group A, the UCM procedure was performed as follows. The neonates were placed below the level of the placenta and the umbilical cord was milked from a distance of 20 cm from the neonate 3 times towards the neonate before cord clamping.¹²

Neonates' data, including gestational age, sex, birth weight, presence or absence of respiratory distress syndrome, intraventricular hemorrhage, and hemodynamically significant patent ductus arteriosus, whole blood cell count, frequency

of sepsis, and the time of hospital stay were obtained from the medical records.

The first eye examinations of each of the infants were performed at the postnatal age of 4 weeks. Follow-up was continued until retinal vascularization was completed. The follow-up schedules were organized depending on the retinal findings.¹⁴ All of the examinations were performed by the same doctor (AK, AS) with indirect ophthalmoscopy with a 20 D lens and scleral depression. The retinal findings were evaluated according to the International Classification of Retinopathy of Prematurity.¹⁵ The patients were grouped as no ROP, mild ROP (stages 1-2 ROP, showed regression), and severe ROP (\geq stage 3, required treatment).

We evaluated the possible correlation between ROP development in UCM group and gestational age, sex, birth weight, presence or absence of respiratory distress syndrome, and presence of sepsis, by using multivariate logistic regression analyses.

Statistical analyses were performed using a commercially available statistical software package (SPSS 15.0 for Windows, SPSS Inc., Chicago, IL, USA). Multivariate logistic regression analyses were used for evaluating the factors related to development of ROP. The t-test, chi-square test, and Fisher's exact test were used. For all tests, the level of significance was set at $P < 0.05$.

RESULTS

A total of 38 neonates received UCM (group A) and 37 received early cord clamping (group B). There were no significant differences in sex, gestational age, and birth weight between the 2 groups (Table 1). Gestational weeks of the patients were similar between the 2 groups (Figure 1).

Hemoglobin levels were not significantly different between the 2 groups (Table 1). There were no significant differences in the rates of sepsis, intrauterine growth retardation, hemodynamically significant patent ductus arteriosus, respiratory distress syndrome, and intraventricular hemorrhage, which are considered as predisposing factors for the development of ROP, between the groups (Table 1, Figure 2).

Four patients in group A and 4 patients in group B were diagnosed with mild ROP disease, which then spontaneously regressed. One patient in group A and 2 patients in group B were diagnosed with stage 3 ROP and received laser photocoagulation treatment. None of the infants were affected by more severe stages of ROP or required further surgical interventions. Data of 1 patient in group A and 4 patients in group B were not included in statistical analyses because of a lack of medical records of ROP examinations. Chi-square tests showed no significant difference in development of ROP and ROP that requires treatment between the 2 groups ($P = 0.778$, $P = 0.621$) We also evaluated, development of ROP

Table 1. Baseline characteristics of the patients.

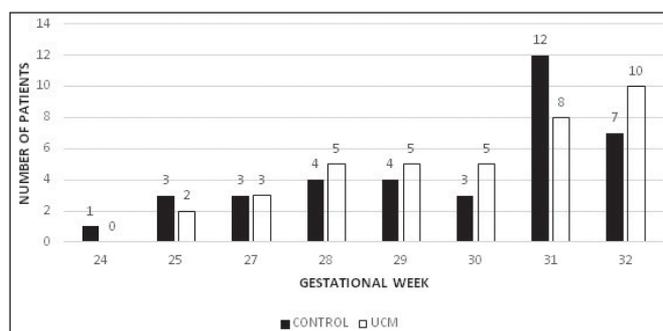
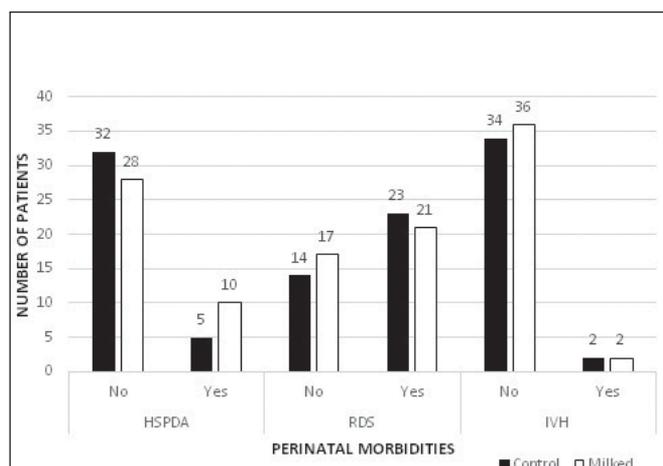
	-/+	ECC group	UCM group	P value
Patients (n)		37	38	
Sex, male (%)		19(%45,2)	23(%54,8)	0,424
GW, <30 (%)		15(%50,0)	15(%50,0)	0.925
Birth weight(grams±SD)		1454,86±394,219	1408,28±387,434	0.607(a)
RDS(N)	-	14	17	0.544(b)
	+	23	21	
HSPDA(N)	-	32	28	0.166(b)
	+	5	10	
IVH(N)	-	35	36	0.956(b)
	+	2	2	
Sepsis(N)	-	24	26	0.742(b)
	Suspected	6	4	
	Proven	7	8	
Hb(g/dl±SD)		16,94±2.20	17.55±2.23	0.234(a)

(a) Two independent samples t-test for continuous data that were normally distributed.

(b) Fisher's exact chi-square test for categorical data.

-: not present, +: present, N: number of patients

ECC: early cord clamping, UCM: umbilical cord milking, GW: gestational weeks, RDS: respiratory distress syndrome, HSPDA: hemodynamically significant patent ductus arteriosus, IVH: intraventricular hemorrhage, Hb: hemoglobin.

**Figure 1.** Distribution of gestational weeks of the patients.**Figure 2.** Distribution of perinatal morbidities.

between the group of infants that divided two groups as gestational age <30 weeks or higher and birth weight <1500gr or higher, but there is no statistically significant difference between groups according to these classification. ($P=0.689$, $P=0.638$)

We didn't find any correlation between ROP development in UCM group and gestational age, sex, birth weight, presence or absence of respiratory distress syndrome, and presence of sepsis by using multivariate logistic regression analyses. (Table 2)

DISCUSSION

Approximately one-quarter of a newborn's blood volume is wasted by clamping the umbilical cord immediately after birth.⁹ Therefore, the World Health Organization and American College of Obstetricians and Gynecologists recommend standard delayed cord clamping in the delivery room for newborns who do not need resuscitation.^{9,16} However, there are concerns about this procedure in neonates needing resuscitation. In such patients, an alternative that can provide the newborn with the desired additional blood volume is called UCM.⁹ In delayed cord clamping, passive transfer of additional blood volume occurs at a slow rate, whereas in UCM, active transfer of additional blood volume occurs at a rapid rate within a short time.¹¹ UCM is a safe procedure, improving hemoglobin levels, and reducing the need for blood

Table 2. Multivariate Logistic Regression Analyses in a model of gestational age, birth weight, gender, development of RDS and sepsis as independent factors and development of ROP as the dependent factor.

	OR	% 95 CI	p
Gestational age			
<30 weeks	reference		
≥30 weeks	1.3	0.3-4.7	0.69
Birth Weight			
<1500 gr	Reference		
≥1500 gr	1.3	0.3-4.9	0,63
Gender			
Male	Reference		
Female	2.3	0.5-9.6	0.23
RDS			
+	reference		
-	1.2	0.3-4.4	0.76
Sepsis			
+	reference		
-	1.4	0.5-3.5	0.43

RDS: respiratory distress syndrome

transfusions, and for circulatory and respiratory support in preterm infants.¹²

Previous studies have shown that, in preterm infants, UCM reduces the number of days of oxygen therapy and results in fewer neonates receiving blood transfusions.^{12,13,17,18} Additionally, in moderate to late preterm neonates, UCM improves hematological parameters (hemoglobin and ferritin) in early infancy.¹⁹ However, a previous study showed that UCM was associated with higher initial hemoglobin values and a lower risk for oxygen requirement, but these improvements did not lead to a reduction in the need for blood transfusion.¹¹ A prospective study including 318 patients showed that UCM was a safe and effective method for improving early hemodynamic stability among neonates who were born at <30 weeks of gestation.²⁰ Additionally, UCM reduced death and/or serious morbidities.²⁰ However, we couldn't find any correlation between ROP development in UCM group and gestational age, sex, birth weight, presence or absence of respiratory distress syndrome, and presence of sepsis.

The pathogenesis of ROP is multifactorial. Blood transfusion increases the risk of ROP in newborns. This affect has been attributed to increased delivery of oxygen, iron, and free radicals of oxygen to the retina.^{7,21,22} The duration of oxygen therapy is also an independent risk factor for ROP.²³

Recently, with improvement in neonatal care, the survival rate of extremely premature infants, who are in the high-risk group for ROP development, has increased.²⁴ With proper

care, most neonates develop a mild degree of ROP, but in some patients, this condition is progressive, needs treatment, and causes morbidity.²⁴ ROP is known as the major cause of blindness in infants.²⁵ Therefore, prevention of ROP has become more important recently. In this retrospective study, we hypothesized that UCM reduces the incidence of ROP because it reduces the need for blood transfusions and oxygen therapy. However, we found no significant correlation between UCM and the development of ROP. In addition, although we couldn't find any significant difference, patients with ROP that requires treatment was higher in non-UCM group. In contrast to previous reports, we did not find any significant reduction in the blood transfusion rate and other comorbidities of neonates who received UCM. Hemoglobin levels were also not significantly different between the 2 groups. These findings might be the reason why we did not find any significant difference in the incidence of ROP between the 2 groups.

The most important limitation of our study is that it was a retrospective study. The cord milking procedure could be better standardized in a prospective study. Training for the milking procedure should be generalized among obstetricians for better outcomes. A second limitation is that the sample size was relatively small and could be increased for more reliable results.

CONCLUSIONS

To the best of our knowledge, this is the first study to focus on the effect of UCM on development of ROP. There

is no correlation between UCM and the incidence of ROP, however patients with ROP that requires treatment was a little higher in non-UCM group. Further investigations, with a prospective design and larger sample size, are required to better understand the effect of the UCM procedure on ROP.

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