Efficacy of Delayed versus Immediate Cord Clamping in Late Preterm Newborns following Normal Labor: A Randomized Control Trial

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Background: *Premature neonates are susceptible to anemic problems with low iron storage. Delayed cord clamping (DCC) has been studied and its beneficial value has been supported by existing research in newborns with very low birth weights. But there were only few data pertinent to late preterm infants.*
Objective: *To investigate the effect of delayed cord clamping (DCC) as compared with immediate cord clamping (ICC) on the hematocrit level at 48 hours in late preterm neonates after vaginal delivery.*
Material and Method: *The design consisted of a randomized controlled trial. One hundred pregnant women who were admitted because of preterm labor (GA 34-36^{+6} week) in active phase were recruited and allocated into two groups, designated as the ICC and DCC groups. The DCC were defined as the case in which patients underwent the umbilical cord clamping at 120 seconds after birth. At 48 hours after delivery, both the hematocrit (Hct) and microbilirubin (MB) levels of newborns were determined. Also, neonatal and maternal complications were recorded.*
Result: *Eighty-six neonates were analyzed. There were no statistical differences in the baseline data of maternal symptoms and newborns between the two groups. Neonates in the DCC group had a significantly higher hematocrit level than the ICC group (55.4% and 47.6%, respectively: p = 0.02). The MB level in the DCC group was also significantly higher than in the ICC group (9.4% and 8.6 mg %, respectively: p = 0.04). However, phototherapy and length of hospitalization in both groups were not different. There were no serious maternal and fetal complications in either group.*
Conclusion: *The DCC procedure could raise the Hct level in the late preterm newborns without serious adverse effects. But more evidence is needed to explore the possible benefit of this procedure.*

Keywords: *Delayed cord clamping, Late preterm, Hematocrit, Microbilirubin*

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All infants experience a decrease in hemoglobin concentration after birth as a consequence of diminished erythropoietin (EPO) levels. For the term infant, a physiologic and usually asymptomatic anemia are observed within 8-12 weeks following birth. However, the anemia effect is more pronounced in very small, premature infants and can lead to several complications, such as intraventricular hemorrhage (IVH), impaired circulatory hemodynamic, neonatal sepsis (especially in severe anemia) and a need for RBC blood transfusions[1-6]. Because of low birth weight, premature infants are required to undergo repeated phlebotomy as a means of monitoring their complications. This amount of blood depletion is estimated to be about 5-10% of the total blood volume[4]. Recently, many procedures have been studied for the purpose of improving neonatal anemia, such as delayed cord clamping, umbilical cord milking and positioning the neonatal infant on the maternal abdomen. Delayed cord clamping (DCC), in which the cord was clamped between 30 to 180 seconds after birth, and umbilical cord milking (UCM), in which blood from cord or placenta is squeezed toward the baby, have been shown to incur an increase in hemoglobin in preterm and term infants[6-11].

In a committee opinion of the American College of Obstetricians and Gynecologists (ACOG) on the timing of umbilical cord clamping after birth,

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participants stated their support for delayed cord clamping in preterm infants. This procedure could reduce incidences of IVH by 50% and improve short-term outcomes, such as necrotizing enterocolitis, blood transfusions and neonatal sepsis[12,13]. There is substantial evidence in newborns with very low birth weight (VLBW) which showed the efficacy and safety of DCC; however, for the late preterm group ($34\text{-}36^{+6}$ week), there is limited data to demonstrate these effects.

The main objective of this investigation was to determine the difference in hematocrit and microbilirubin levels between the immediate cord clamping (ICC) and delayed cord clamping (DCC) groups in late preterm neonates who were vaginally delivered.

Material and Method

This randomized controlled trial was conducted in the Department of Obstetrics and Gynecology, Thammasat University Hospital (in Pathumthani, Thailand), between July of 2014 and April of 2015. This investigation was approved by the Institutional Review Board of the Faculty of Medicine at Thammasat University with the Thai Clinical Trial Registry (MTU EC OB 2-035/57). The inclusion criteria involved pregnant women whose ages were between 18-45 years, and who were admitted because of preterm labor in the active phase with gestational ages (GA) ranging from $34\text{-}36^{+6}$ weeks. Preterm labor in the active phase is defined as regular uterine contractions occurring at least 4 times within a 20-minute interval with cervical dilatations of more than 4 cm. Accurate GA assessment was determined by antenatal ultrasonograms during the first or second trimester. The exclusion criteria were pregnancy with thalassemia syndrome, preeclampsia, gestational diabetes mellitus (GDM), renal impairment, placental abnormalities, fetus with major congenital anomalies, multiple gestations, instrumental delivery and-or abnormal fetal tracing (severe fetal bradycardia, fetal distress and non-reassuring fetal heart rate).

One hundred participants were enrolled in this investigation. Signed written informed consent was obtained after counseling. Subjects were randomized and divided into two groups: a control group, based on immediate umbilical cord clamping (ICC); and a study group, based on delayed umbilical cord clamping (DCC).

Simple randomization was used. Sealed envelopes containing numbers which had been generated by a statistical computer program were placed in a box. The first attending physician at the labor room picked up a sealed envelope, which would then be attached to the patient's medical record in an intact manner and opened only at the start of the second stage of labor. The control group was defined by the application of ICC as a standard procedure. The study group was defined as DCC within 2 minutes after vaginal delivery. A stopwatch was used for time control. Following birth, the babies were placed at the same level of maternal body trunk. The babies in the DCC group were wrapped with a sterile towel. During the process, care was taken not to allow the umbilical cord to be overstretched. Neonates from either group were transferred to the newborn unit and underwent routine standard management by a pediatrician who attended the newborn unit. The pediatrician was notified prior to transfer of the baby to the newborn unit. Neonatal wellbeing was evaluated by the Apgar scoring system at 1 and 5 minutes. Respiratory rate, body temperature and oxygen saturation in the labor rooms were observed for each newborn for 2 hours.

The collected data were composed of demographic data, length of stay in the hospital (LOS), hematocrit (Hct) and microbilirubin (MB) levels at 48 hours after birth, and maternal and neonatal complications. Venous blood samples were collected in two capillary tubes for Hct and MB evaluation. An additional 1 ml of venal blood was also taken and preserved with K3EDTA in any case where the baby's hematocrit level was higher than 65%. The complete blood count was performed to confirm the existence of any polycythemia.

The sample size was calculated on the basis of Ultee's trial[2]. The study required the participation of 50 infants in each group, including a 20% attrition rate that typically follows such a study. It gave a desired power of 80%, α and β level of 0.05 and 0.20, respectively. Statistical analysis was computed using the STATA program. Analysis of the data continuous was performed through the unpaired t-test or Mann-Whitney U test as appropriate. Comparison of categorical data was performed through the Chi-squared test, according to which method was the more applicable. A p-value <0.05 was understood as significant.

Results

One hundred participants were enrolled in the investigation. The cases were randomized and divided into a DCC and ICC group. Each group comprised 50 cases. Eight and six cases in the DCC and ICC groups, respectively, dropped out from the study. A total of 86 infants were analyzed. Demographic data consisted of maternal age, parity, body-mass index, maternal Hct, estimated blood loss and postpartum hemorrhage. The two groups revealed no significant differences in these baseline characteristics, as shown in Table 1.

Neonatal outcomes data consisted of neonatal birth weight, Apgar score, length of stay in hospital and Hct and MB at 48 hours after birth. The Hct level 48 hours after birth in the DCC group was significantly higher than that of the ICC group (55.4 and 47.6%, respectively: $p = 0.02$). Three infants in the ICC group were anemic (Hct <40%). Hemolysis was the cause of anemia in these infants. There were no blood transfusions in this study. The MB level at 48 hours in the DCC group was significantly higher than that of the ICC group (9.4 and 8.6 mg%, respectively: $p = 0.04$). Each group had only one case of polycythemia. There were no differences in phototherapy or length of stay between the two groups. Likewise, there were no statistical differences of mean birth weight, GA at birth, percentage of newborns with Apgar score at 1 and 5 minutes between the two groups, as presented in Table 2. Also, there were no serious maternal and neonatal complications in the study group.

Discussion

The results of the present study, which has been designed as a randomized controlled trial, demonstrated the significant effect of DCC compared to ICC. The mean of the Hct and MB levels in the DCC group was higher than in the ICC group with statistical significance. This result was consistent with the Ultee et al and Ranjit et al studies[2,14]. However, the interval of cord clamping, 180 seconds, in the Ultee et al study was longer than in this report. Several investigators had selected a variety of timing for cord clamping in their studies, ranging from 30 to 180 seconds[1-7,9-11]. Strauss et al reported that the sixty seconds of delayed cord clamping had not significantly raised the Hct[3]. The postulated mechanism of this effect might be that the blood pool from the placenta could not completely transfuse to the newborn infant in such a very short interval of time. A delay in cord clamping of preterm neonates resulted in an increase of 10-28 ml/kg after vaginal delivery[15]. This study had selected the interval of 120 seconds in delayed cord clamping, which could possibly be enough time to achieve this benefit. The 120-seconds interval was also similar to the DCC time applied in the study of Ranjit et al[14], in which it was shown that an appropriate DCC time could significantly increase the mean level of Hct of newborn neonates at 24 hours after delivery. Moreover, their results showed the sustained beneficial long-term effect of iron storage at 6 weeks, together with the ferritin-level measurement during the neonatal period.

The MB level in neonates at 48 hours after

Table 1. Maternal baseline characteristics

Characteristics	ICC (n = 44)	DCC (n = 42)	*p*-value
Age (year)	28.7±5.0	26.2± 6.2	0.06*
Body weight (kg)	61.8±10.4	62.7±10.3	0.90*
BMI (kg/m²)	24.3±4.4	23.7±3.7	0.29*
Parity			0.83**
Nullipara	23 (52.27)	23 (54.76)	
Multipara	21 (47.73)	19 (45.24)	
Antenatal care			0.15**
≥4 times	42 (95.45)	36 (85.71)	
<4 times	2 (4.55)	6 (14.29)	
Maternal Hct (%)	34.7±3.1	35.1±4.0	0.42*
Blood loss (ml)	200 (150-300)	200 (150-300)	0.45**

ICC = immediate umbilical cord clamping; DCC = delayed umbilical cord clamping; BMI = body mass index; Hct = hematocrit
* Data as mean ± SD, using unpaired t-test; ** Nonparametric data as median with max-min and number with percentage, using Mann-Whitney U test and Chi-squared test, respectively
$p \leq 0.05$, statistical significant

Table 2. Neonatal characteristics and studied outcomes

Neonatal outcomes	ICC (n = 44)	DCC (n = 42)	*p*-value
Birth weight (gm)	2,528.8±239.9	2,663.8±260.0	0.74*
Gestational age (week)	36.0±0.8	35.7±1.0	0.10*
Apgar score			NA
1 min <7	0	0	
5 min <7	0	0	
Hct at 48 hour (%)	47.6±5.8	55.4±4.7	0.02*+
MB at 48 hour (mg/dl)	8.6±2.1	9.4±1.3	0.04*+
Jaundice	8 (18.2)	5 (11.9)	0.42**
Polycythemia	1 (2.3)	1 (2.3)	1.00**
Phototherapy	8 (18.2)	5 (11.9)	0.42**
Hypothermia	0	0	NA
Hypoglycemia	3 (6.8)	3 (7.1)	1.00**
Early neonatal sepsis	4 (9.1)	4 (9.5)	1.00**
Respiratory distress	4 (9.1)	3 (7.1)	1.00**
LOS (hour)	53 (45-288)	52.5 (49-288)	0.90**

ICC = immediate umbilical cord clamping; DCC = delayed umbilical cord clamping; Hct = hematocrit; MB = microbilirubin; LOS = length of stay in hospital

* Data as mean ± SD, using unpaired t-test; ** Nonparametric data as median with max-min and number with percentage, using Mann-Whitney U test and Chi-squared test, respectively

+ $p \le 0.05$, statistical significant

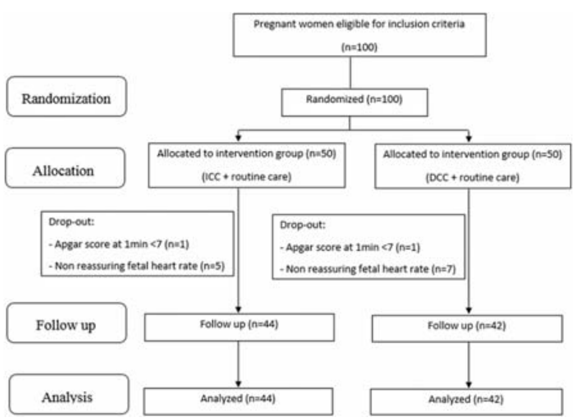

Fig. 1 The Consort 2010 flow diagram of study.

delivery was one of the major outcomes in the study and an indicator of the safety of the procedure. Moreover, the MB level has been routinely investigated in every neonate at 48 hours after birth. Bilirubin is the degradation product of red blood cells. The MB level indicated the destruction rate of fetal red blood cells. A higher hematocrit level could cause a higher MB level. From the previous literatures(2-4), MB in DCC group was higher than in the control group without statistical difference. Their reports were not consistent with the results in this study, which showed a marginally significant higher MB in delayed cord clamping than in the ICC group (9.4 and 8.6 mg/dl, respectively: $p = 0.04$). However, the rising level was not so high as to be harmful. The incidence rate of jaundice and phototherapy in neonates were comparable in both groups. The MB level in late preterm newborns that needs to have phototherapy is 11 mg/dl, according to American Academy of Pediatrics (AAP) guidelines(16). Maternal complications, including blood loss, rate of immediate postpartum hemorrhage and duration of hospital stay, did not differ between the two groups. The results were similar to those of previous studies, in that the delayed cord clamping had not increased the rate of maternal complications(1-11,14). Neonatal complications were not different in terms of Apgar scores at 1, 5 minutes and length of stay. Also, rates of hypothermia, hypoglycemia, neonatal sepsis and respiratory distress did not increase. These parameters implied a preliminary conclusion that the procedure is safe. However, determination of complication outcomes was not our main objective. The adverse effects warrant further investigation in a larger population.

The ACOG recommend that the delayed cord clamping be applied to newborns with very low birth weight for the benefits of increasing blood volume, reducing the need of blood transfusions and decreasing incidences of IVH[12,13]. Use of DCC is also recommended because this method is simple so that midwives and labor coaches can be easily trained in its proper use. Additionally, no additional costs are incurred nor are any special instruments needed. Our findings suggested that the possible benefits are not accompanied by serious complications during late preterm. Also, two minutes of delayed cord clamping could be a sufficient length of time as well as be more practical in implementing DCC since, in late preterm, newborns are prone to hypothermia if they are unnecessarily exposed to room temperature.

There were some limitations of the study we conducted. Firstly, there was no long-term follow-up of the main outcomes. Secondly, Hct in its use as a determinant marker might not best represent the iron storage in newborns. The ferritin is a better surrogate of this storage as presented in prior reports. Thirdly, there were some participants who dropped out so that the data applicable to these cases could not be analyzed.

Conclusion

The DCC procedure could raise Hct levels in the late preterm newborns. These higher levels could possibly increase the iron stage in their later life. However, the procedure needs to be investigated further in order to discover its real beneficial long-term effects.

What is already known on this topic?

A physiologic change in the neonatal red cell mass is observed at 8-12 weeks after birth. This adaptation sometimes marks a decrease in hemoglobin concentration. However, an anemia effect is more pronounced in small or premature infants. There is strong evidence in newborns with very low birth weights which shows the efficacy and safety of the DCC technique in increasing hemoglobin levels. The ACOG stated its support of DCC for the benefits it offers to preterm infants.

What this study adds?

The DCC procedure could significantly raise the Hct level in late preterm newborns. This effect could possibly increase their iron storage in later life. This technique did not exacerbate maternal and neonatal complications. It had the advantage of being a simple method that can be easily taught and a safe procedure that involves no additional costs or special instrumental requirements.

Ethical approval

The study was approved by the Ethical Committee, Faculty of Medicine, Thammasat University, study protocol numbers MTU EC OB 2-035/57.

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Potential conflict of interest

None.

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การศึกษาประสิทธิผลของการชะลอการตัดสายสะดือทารกครรภ์ใกล้ครบกำหนดที่คลอดทางช่องคลอดเปรียบเทียบกับการตัดสายสะดือตามวิธีมาตรฐาน: การทดลองแบบสุ่ม

รสิตา สาแหละ, ชำนาญ แท่นประเสริฐกุล, จรินทร์ทิพย์ สมประสิทธิ์, กรณ์กาญจน์ ภมรประวัติธนะ, คมสันติ์ สุวรรณฤกษ์

ภูมิหลัง: *ทารกที่คลอดก่อนกำหนดมีความเสี่ยงต่อการเกิดภาวะซีดและมีการสะสมของธาตุเหล็กน้อย เมื่อแรกคลอดมีการศึกษาถึงประโยชน์ของการชะลอการตัดสายสะดือทารกหลังคลอดในทารกที่น้ำหนักแรกเกิดน้อย (<1,000 กรัม) พบว่าช่วยลดความเสี่ยงดังกล่าวได้ รวมทั้งมีรายงานถึงประโยชน์ ด้านอื่นๆ ด้วยแต่ยังมีการศึกษาที่น้อยอยู่ ในกลุ่มทารกใกล้ครบกำหนด (34-36^{+6} สัปดาห์)*

วัตถุประสงค์: *เพื่อศึกษาประสิทธิผลของการชะลอการตัดสายสะดือที่เวลา 120 วินาทีหลังคลอด ในทารกคลอดครรภ์ใกล้ครบกำหนด (34-36^{+6} สัปดาห์) ที่คลอดทางช่องคลอด เปรียบเทียบกับการตัดสายสะดือตามวิธีมาตรฐาน เพื่อประเมินความแตกต่างของระดับความเข้มข้นเลือดของทารกหลังคลอด 48 ชั่วโมง*

วัสดุและวิธีการ: *เป็นการศึกษาวิจัยเปรียบเทียบแบบสุ่ม ในสตรีตั้งครรภ์เดี่ยว จำนวน 100 ราย ที่ได้รับการวินิจฉัยเป็นภาวะเจ็บครรภ์คลอดก่อนกำหนด อายุครรภ์ 34-36^{+6} สัปดาห์และไม่มีภาวะแทรกซ้อน แบ่งเป็น 2 กลุ่ม โดยการสุ่มคือกลุ่มตัดสายสะดือตามวิธีมาตรฐาน (ในระยะเวลา 30 วินาที) (กลุ่ม ควบคุม) และกลุ่มชะลอการตัดสายสะดือ ที่ระยะเวลา 120 วินาที (กลุ่มทดลอง) หลังคลอดปกติทางช่องคลอด ประเมินผลโดยวัดความเข้มข้นเลือดของทารกที่ 48 ชั่วโมงหลังคลอด และติดตามภาวะแทรกซ้อนมารดาและทารก*

ผลการศึกษา: *สตรีตั้งครรภ์จำนวน 86 ราย แบ่งเป็นกลุ่มตัดสายสะดือตามวิธีมาตรฐาน 44 คน และกลุ่มชะลอการตัดสายสะดือ 42 คน พบว่าข้อมูลพื้นฐานของทั้งสองกลุ่ม ได้แก่ อายุเฉลี่ย น้ำหนักก่อนตั้งครรภ์ ดัชนีมวลกายก่อนตั้งครรภ์ จำนวนครั้งการตั้งครรภ์ จำนวนครั้งการฝากครรภ์ ระดับความเข้มข้นเลือดของมารดา และปริมาณเลือดที่เสียระหว่างคลอด ไม่มีความแตกต่างกันอย่างมีนัยสำคัญ เมื่อทารกอายุได้ 48 ชั่วโมงหลังคลอด พบว่าค่าความเข้มข้นเลือดในกลุ่มทดลองสูงกว่ากลุ่มควบคุม อย่างมีนัยสำคัญทางสถิติ คือ ร้อยละ 55.4 และ 47.6 ($p = 0.02$) ระดับสารเหลืองในหลอดเลือดดำในกลุ่มทดลองสูงกว่าในกลุ่มควบคุมอย่างมีนัยสำคัญทางสถิติเช่นเดียวกัน คือ เท่ากับ 9.4 และ 8.6 mg % ($p = 0.04$) และไม่พบความแตกต่างอย่างมีนัยสำคัญทางสถิติของภาวะเหลือง การส่องไฟรักษาและระยะเวลาการนอนโรงพยาบาลในทั้งสองกลุ่ม ไม่มีภาวะแทรกซ้อนที่รุนแรงทั้งในมารดาและทารก*

สรุป: *การชะลอการตัดสายสะดือในทารกอายุครรภ์ใกล้ครบกำหนด (34-36^{+6} สัปดาห์) ระยะเวลา 120 วินาทีหลังการคลอดปกติ มีประโยชน์ในการเพิ่มปริมาณเลือดแก่ทารกที่ 48 ชั่วโมงแรกของทารก โดยที่ไม่เพิ่มภาวะแทรกซ้อนต่อมารดาและทารก*