Original Article

Effect of Delayed Cord Clamping Reduced Anemic Outcome in Preterm Neonate

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Objective: To compare the effects of immediate versus delayed cord clamping on neonatal outcomes in preterm neonates of gestational age of 32 to 36^{+6} weeks, and maternal outcomes.

Materials and Methods: A randomized controlled trial was conducted in the Obstetrics and Gynecology Department at Bhumibol Adulyadej Hospital, in Bangkok, Thailand. The study compared the effects of immediate to delayed cord clamping at 60 seconds among preterm neonates born between 32 weeks, 0 day and 36 weeks, 6 days of gestation between August and October 2018.

Results: The mean age of the participants was 26 years old, and half of the cases were nulliparous. One hundred ten women were randomly separated into two equal groups (n=55). Delayed cord clamping at 60 seconds increased hematocrit levels (Hct) in both two (p=0.004) and 48 (p<0.001) hours after delivery compared to the immediate cord clamping group. There were no differences in exposing the neonate to hypothermia, hypoxemia, Apgar score at 1-minute, polycythemia, intraventricular hemorrhage, hyperbilirubinemia, length of stay in hospital, and affecting the process of resuscitation. There were no statistical differences between the two groups in maternal outcomes such as retained placenta and postpartum hemorrhage.

Conclusion: Delayed cord clamping at 60 seconds increased Hct in the newborn at two to 48 hours after birth. There was no significant difference in adverse maternal and neonatal complications within both groups.

Keywords: Delayed cord clamping, Hematocrit, Preterm

Received 18 December 2018 | Revised 18 February 2019 | Accepted 18 February 2019

J Med Assoc Thai 2021;104(5):695-700

Website: http://www.jmatonline.com

Anemia is a common clinical problem worldwide found in both children and adults. Prevalence of anemia among women of reproductive age was 30% and up to 40% in pregnant women[1-3]. The anemia in children is around 50%[4]. All infants universally experience a decrease in hemoglobin (Hb) or hematocrit level (Hct) that results in varying degrees of anemia. Hct measurement is easy and requires only small amount of infant blood.

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How to cite this article:

Inploy N, Prommas S, Smanchat B, Pongrojpaw D, Bhamarapravatana K, et al. Effect of Delayed Cord Clamping Reduced Anemic Outcome in Preterm Neonate. J Med Assoc Thai 2021;104:695-700.

doi.org/10.35755/jmedassocthai.2021.05.9614

Anemia in preterm infant is a pathophysiological process with larger and faster drop in Hct. Consequently, blood transfusion and other human blood recombinants are needed[5]. The cause of anemia varies based upon the age at presentation. In neonates and young infants, immune hemolytic diseases, infection, and hereditary disorders are the common causes of anemia[6]. In older children, acquired causes of anemia were more likely the cause of anemia, particularly from iron deficiency anemia and thalassemia.

The rapidity that anemia develops, and its ultimate severity are determined by a combination of multiple physiologic and non-physiologic processes[7]. The major impact of anemia is tissue hypoxia, resulting in both compensatory responses and acute or chronic consequences including poor growth, delayed brain development, decreased activity, and limited cardiovascular reserve[8].

It has been a general approach to clamp the newborn umbilical cord immediately in the birth

process after the time of birth and fluid suction out of the mouth and nose. However, today the obstetrician prefers to delay clamping the umbilical cord for a few minutes after initial breaths taken by the newborn. The baby will get extra blood volume that flows from the placenta to the baby. By doing this, it helps the iron storage increment and anemia decrement in newborn[9].

However, contemporary optimal timing for clamping the cord and the position of the newborn to be held before clamping the cord remain uncertain. The objective of the present study was to compare the immediate cord clamping (ICC) and delayed cord clamping (DCC) on how they potentially affect the health of newborns, especially for anemia in preterm infant.

Materials and Methods

The present randomized controlled trial was conducted in Obstetrics and Gynecology Department at Bhumibol Adulyadej Hospital, Bangkok, Thailand, comparing ICC with DCC among preterm neonates born between 32 weeks 0 days and 36 weeks 6 days gestation between August 2018 and October 2018. This protocol was approved by the Hospital Ethics Committee, Bhumibol Adulyadej Hospital (IRB BAH 77/60).

Physicians and research nurses approached candidates for the trial and obtained formal written consents from those who elected to participate before randomization into the study and after fully disclosing the nature, potential benefits, and risks of participating in the trial. The inclusion criteria were viable singleton preterm pregnancy at 32 to 36^{+6} weeks of gestation and underwent vaginal delivery at the labor room or cesarean delivery at the operating room. Pregnant women were excluded if they had fetuses with major severe congenital anomalies or chromosomal abnormalities, multifetal gestations, maternal coagulopathy, or maternal anemia (Hct of less than 30%), placenta previa or placenta abruption, fetal non-reassuring or fetal distress, non-vigorous neonate, and denied participation.

The primary outcome of the present study was Hct at two and 48 hours of life. The main secondary outcomes were the need of blood transfusion, Apgar score, jaundice requiring phototherapy, polycythemia, length of stay in the hospitals, and mortality rate. Maternal outcome included postpartum hemorrhage and retained placenta.

Allocation sequence was generated by simple randomization using a computer. The allocation sequence was concealed by using sequentially numbered, opaque, sealed envelopes kept in a central location on labor and delivery unit.

Participants were simply randomized into two groups, ICC and DCC group. The intention of ICC or DCC was to clamp the umbilical cord within 5 or 60 seconds of delivery, respectively. Before umbilical cord clamping, neonates were held at the same level of the introitus in vaginal delivery or operating table in case of cesarean delivery. Circulating nurse would countdown the time for cord clamping by standard digital clock.

The newborn received an ICC newborn care after birth by pediatrics residents following the guidelines for neonatal resuscitation recommended by the American Academy of Pediatrics and the American Heart Association. For the neonates in the DCC group, their cares included provision of warmth using a warming mattress, bulb suction, and stimulation as appropriated.

The data collection included Apgar score, oxygen saturation, body temperature, Hct, serum bilirubin, rate of phototherapy, blood transfusion and length of stay in the hospital. Vital signs, maternal Hct, estimated blood loss, length of third stage of labor, the maternal complication such as postpartum hemorrhage, and retained placenta indicating the need for manual removal of placenta were also recorded.

Sample size

Sample size was calculated following Elimian et al's work in 2014[10]. One hundred six cases were the number of appropriated cases for statistical significance. For prevention of unexpected exclusion and drop out sample, the authors recruited an extra ten percent of the calculated sample size. Therefore, 116 cases were recruited in the present study.

Statistical analysis

The data were performed using the PASW Statistics for Windows, version 18.0 (SPSS Inc., Chicago, IL, USA) for analysis. The categorical variables with the chi-square test or Fisher's exact test were used as appropriated. The result was reported as percentages or means, and standard deviations (SD). Statistical significance was reported at p-value less than 0.05.

Results

One hundred ten women were equally randomized into ICC and DCC groups as depicted in the study profile as represented in Figure 1. The two groups

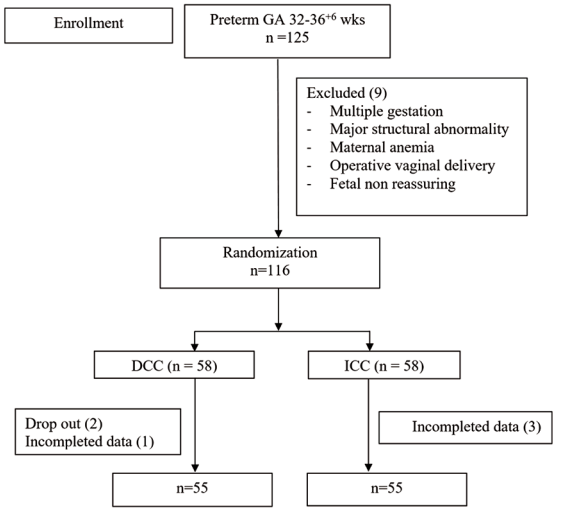

Figure 1. Flow of recruitment of study participants.

were similar with respect to baseline characteristics including maternal age, gestational age, gravida, ethnicity, initial weight and weight at delivery, height, length of third stage of labor, and estimated blood loss. There was only one case each in maternal complication, namely chorioamnionitis, retained placenta, and postpartum hemorrhage detected in DCC group as demonstrated in Table 1.

The mean Hct after two and 48 hours after birth of DCC were significantly higher than that of ICC as shown in Table 2. Neonatal characteristics included fetal weight, gender, Apgar score at 1-minute, initial rectal temperature, oxygen saturation at 5-minute, and admission at routine newborn unit or neonatal intensive care unit (NICU) were not significantly different between the two groups.

The mean micro-bilirubin of ICC was higher than that of DCC (9.08 compared to 8.74, p=0.497). The proportion of neonatal jaundice that brought to phototherapy in ICC was slightly higher than DCC without statistical difference (41.8% and 36.4%, p=0.558).

There was no case of necrotizing enterocolitis (NEC) in the present study. There was no difference in consequent neonatal outcomes in both ICC and DCC such as intraventricular hemorrhage (IVH) (3/0, p=0.243), respiratory distress syndrome (12/8, p=0.323), and late neonatal sepsis (6/3, p=0.489).

The newborn length of stay in hospital of ICC was greater than DCC (9.3 versus 6.7, p=0.286). The present study found no statistically significant difference between neonatal mortality rate in the study groups. There was only one infant mortality case in

Table 1. Maternal characteristics (n=110)

Characteristics	Early (n=55); n (%)	Delayed (n=55); n (%)
Age (years); mean±SD	26.51±7.65	25.47±5.78
GA	34 weeks	35 weeks
Gravida		
Nulliparous	28 (50.9)	26 (47.3)
Multiparous	27 (49.1)	29 (52.7)
U/D	4 (7.3)	6 (10.9)
Ethnicity		
Thai	49 (89.1)	55 (100)
Other	6 (10.6)	0 (0.0)
ANC		
No	11 (20.0)	9 (16.4)
1 to 5 time	12 (21.8)	9 (16.3)
>5 times	32 (58.2)	37 (67.3)
BW (kg); mean±SD		
1st ANC	59.01±16.47	53.56±9.33
Delivery	68.94±17.12	64.74±10.55
Height (cm); mean±SD	158.25±6.89	158.24±5.48
Tobacco use	5 (9.1)	2 (3.6)
Alcohol use	6 (10.9)	1 (1.8)
Drug abuse	3 (5.5)	2 (3.6)
Dexamethasone		
No	20 (36.4)	13 (23.6)
1 to 3 doses	28 (50.9)	36 (65.5)
4 doses	7 (12.7)	6 (10.9)
Antibiotic	39 (70.9)	35 (63.6)
Maternal Hct; mean±SD		
1st ANC	35.20±3.55	35.70±3.63
Delivery	36.35±3.38	36.20±3.84
Clinical diagnosis		
Preterm labor	31 (56.4)	37 (67.3)
Preterm PROM	15 (27.3)	13 (23.6)
Preeclampsia	0 (0.0)	1 (1.8)
Other	9 (16.4)	4 (7.3)
Route of delivery		
Vagina	45 (81.8)	46 (83.6)
Cesarean	10 (18.2)	9 (16.4)
3rd stage of labor; mean±SD	7.15±5.11	8.71±6.92
Total blood loss; median (P25, P75)	300 (150, 300)	300 (150, 400)
Chorioamnionitis	0 (0.0)	1 (1.8)
Retained placenta	0 (0.0)	1 (1.8)
PPH	0 (0.0)	1 (1.8)

GA=gestational age; U/D=underlying disease; BW=body weight; Hct=hematocrit; ANC=antenatal care; PROM=premature rupture of membrane; PPH=postpartum hemorrhage; SD=standard deviation

Table 2. Neonatal outcome (n=110)

Characteristics	Early (n=55); n (%)	Delayed (n=55); n (%)	p-value
BW (g); mean±SD	2,437.00±530.38	2,597.29±417.60	0.081
Sex			
Male	36 (65.5)	32 (58.2)	0.432
Female	19 (34.5)	23 (41.8)	
Apgar at 1 minute			1.000
>7	54 (98.2)	54 (98.2)	
≤7	1 (1.8)	1 (1.8)	
Admission			0.844
Ward	34 (61.8)	35 (63.6)	
NICU	21 (38.2)	20 (36.4)	
BT; mean±SD	36.58±0.48	36.50±0.45	0.395
O_2 sat; mean±SD	89.71±6.01	89.89±7.29	0.887
Hct; mean±SD			
2 hours	50.34±6.19	53.81±6.02	0.004
48 hours	48.23±6.82	52.60±5.75	<0.001
Blood transfusion	0 (0.0)	3 (5.5)	0.243
Ionotropic	1 (1.8)	2 (3.6)	1.000
CPR	0 (0.0)	0 (0.0)	NA
Phototherapy	23 (41.8)	20 (36.4)	0.558
Polycythemia	1 (1.8)	2 (3.6)	1.000
MB; mean±SD	9.084±0.33	8.74±0.35	0.497
ICH	3 (5.5)	0 (0.0)	0.243
RDS	12 (21.8)	8 (14.5)	0.323
Surfactant	4 (7.3)	0 (0.0)	0.118
NEC	0 (0.0)	0 (0.0)	NA
Late onset sepsis	6 (10.9)	3 (5.5)	0.489
LOS; median (P25, P75)	3 (2, 18)	3 (2, 5)	0.286
Mortality	1 (1.8)	0 (0.0)	1.000

BW=body weight; NICU=neonatal intensive care unit; BT=body temperature; O_2 sat=oxygen saturation; Hct=hematocrit; CPR=cardiopulmonary resuscitation; MB=micro bilirubin; ICH=intracranial hemorrhage; RDS=respiratory distress syndrome; NEC=Necrotizing enterocolitis; LOS=length of stay in hospital; SD=standard deviation; NA=not available

p<0.05 is statistical significance

ICC group. It had cardiac arrest after the delivery, which not related with clamping cord.

Discussion

The present random controlled trial of ICC and DCC recruited 110 infants of age of 32 to 36^{+6} weeks of gestation. Benefit of delayed umbilical cord clamping in term of Hct increment was still questionable. The results from the present study seem similar to some previous studies on effect of DCC as shown in Table 3.

Elimian et al's and Ruangkit et al's work[10,11] reported Hct of DCC was higher than early cord clamping. Both works were conducted in newborn cases with gestation age less than 34 weeks. Infant mortality rate in both works was around five percent. The present study showed the same Hct increment that is supported by Elimian et al's and Ruangkit et al's work. The infant mortality rate in the present study was lower than Elimian et al's and Ruangkit et al's work. In regards to the respiratory complication of preterm birth, the present study recruited the newborn age between 32 and less than 37 weeks. Mean newborn age in the present study was higher than Elimian et al's and Ruangkit et al's work at 35, 30, and 29 weeks, respectively.

In Thailand, Mungkornkaew and Siwadune's work[12] showed that Hb levels in 120 seconds of DCC was higher than ICC in both term and preterm singleton. This result was consistent with the Salae et al's study[13]. Mungkornkaew et al's and Salae et al's studies selected 120 seconds for DCC interval, which is longer than the present study. Mean fetal age of Mungkornkaew et al's and Salae et al's literatures were 37 and 36 weeks, respectively. The mean fetal age of the present study was only 35 weeks. Both Mungkornkaew et al's and Salae et al's work had collected only vaginal delivery, while the present study collected both vaginal and cesarean delivery.

Recent study of Chiruvolu et al[14] from USA reported that mean Hct of DCC was higher than ICC. His work recruited the newborn cases with mean age of 33 weeks. There was no fetal death in their study.

Timing of delayed umbilical cord clamping was not exactly defined. There were 30, 45, 60, and 120 second intervals in all six studies[10-13,15,16]. Adverse outcomes of both ICC and DCC had no significant difference. However, the present study selected 60 seconds to delay cord clamping due to appropriate time to practice. The data reported the DCC 60 seconds significantly increased Hct levels more than ICC at two and 48 hours after delivery.

The number of newborns that underwent delayed umbilical cord clamping and needed phototherapy was slightly higher than the ICC umbilical cord clamping group without statistical difference[13,15]. Mungkornkaew and Siwadune's work reported higher phototherapy needed by newborn in DCC group compared to ICC group[12]. However, in the present study, the incidence of jaundice requiring phototherapy in both ICC and DCC groups were slightly higher than the previous report (41.8% and

Table 3. Comparing data the umbilical cord clamping from previous studies

Characteristics	First author						
	Elimian*	Ruangkit*	Mungkornkaew*	Salae*	Chiruvolu*	Fenton*	Present study*
Year	2014	2015	2015	2016	2017	2018	2018
Country	USA	USA	THA	THA	USA	USA	THA
Design	RCT	Cohort	RCT	RCT	Cohort	RCT	RCT
Number	101/99	150/150	100/100	44/42	109/87	260/94	55/55
GA (weeks)	24 to 34	<34	34 to 42	34 to 36^{+6}	<35	23 to 36	24 to 36^{+6}
Mean GA (weeks)	30	29	37	36	33	32	35
Age (years)	25.8/25.3		26.3/24.1	26.2	27.6/28.9		26.5/25.4
Clamping time							
Immediate	<5	<30	60	<120	<60	<15	<5
Delayed	30	≥30	120	120	60	45 to 60	60
Route	Vg, C/S	Vg, C/S	Vg	Vg	Vg, C/S		Vg, C/S
PPH			1/0		0.9/0		0/1.8
Chorioamnionitis	19/16.2				3.7/0		0/1.8
Apgar at 1 minute							
>7	51/48%						1.8/1.8
≤7	45/55	37/28					
Hct at 2 hours					45.7/49.1		50.3/53.8
Hct at 48 hours	47.4/51.3	44/46	51.4/53.1	47.6/55.4			48.2/52.6
MB		9.6/8.7	9.8/12.4	8.6/9.4	8.7/8.8		9.0/8.7
Phototherapy			0/8.4	18.2/11.9	53.3/50		41.8/36.4
IVH							
Death	5/4	4/4					1.8/0
LOS		55/48	2/2.33	2.2/2.1	19/17		9.3/6.7

USA=United States of America; THA=Thailand; RCT=randomized controlled trial; GA=gestational age; PPH=postpartum hemorrhage; Vg=vaginal delivery; C/S=cesarean delivery; Hct=hematocrit; MB=micro bilirubin; IVH=intraventricular hemorrhage; LOS=length of stay in hospital

* Immediate cord clamping/delayed cord clamping

36.4%, respectively). The comparison of neonatal jaundice rate that required phototherapy is presented in Table 3.

Chiruvolu et al showed that the delayed umbilical cord clamping was efficacious in reducing NICU admission[14]. In year 2018, Fenton and co-workers reported that the rate of IVH of DCC was statistically less than that of ICC[16]. The Fenton et al's IVH result was consistent with the Brocato et al's study[15].

DCC for 60 seconds had no significant impact on maternal complications such as chorioamnionitis, retained placenta, and postpartum hemorrhage. This investigation suggested that DCC method was a relatively safe method for participating mothers. These participating mothers seemed to be mostly of late preterm gestation. Fetus in these conditions were normally robust and healthy by nature. Delayed umbilical cord clamping in preterm candidates was recommend as a future research study because the neonate benefit as shown in the present investigation would probably enhance neonate outcome in the preterm population as well.

Conclusion

Delayed umbilical cord clamping for 60 seconds increased Hct in the newborn at two and 48 hours after birth without exposing neonate to serious neonatal outcomes. There was no significant difference on neonatal and maternal morbidity.

What is already known on this topic?

Anemia in preterm infant is a common health problem worldwide. Delayed umbilical cord clamping is a procedure that could raise the Hct and decrease the development of anemia in both term and preterm infants. Some study showed that the DCC increased risk for neonatal complication. The optimal timing for clamping the cord remains uncertain.

What this study adds?

Several studies showed statistically significant higher Hct in DCC. This study agreed with those findings in preterm infants. The 60 seconds cord clamping is a preferred interval compared to other durations. Consequently, 60 seconds DCC is a relatively safe procedure for participating mothers and their babies.

Acknowledgement

The authors would like to thank the staff of the Department of Obstetrics and Gynecology, Bhumibol Adulyadej Hospital for their suggestion and cooperation in this research. In addition, the authors would like to express sincere appreciation to Amphol Saisiriwachakul for his statistical assistance. The trial was registered in Thai Clinical Trials Registry (TCTR). Study ID: TCTR20180817001 (http://www.clinicaltrials.in.th).

Conflicts of interest

The authors declare no conflict of interest.

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