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Timing of umbilical cord clamping and neonatal jaundice in singleton term pregnancy

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ABSTRACT

Background: Delayed cord clamping was not adopted widely in China because of the potential effect of neonatal hyperbilirubinemia, jaundice and polycythemia, and the optimal cord clamping time remained controversial.
AIM: To assess the effect of delayed cord clamping versus early cord clamping on neonatal jaundice for term infants.
Study design: This retrospective study included 1981 mother-infant pairs, who were assigned to early cord clamping groups (n = 1005) and delayed cord clamping group (n = 949). The delayed cord clamping included three subgroups (30–60 s, 61–90 s, 91–120 s). The main outcomes were transcutaneous bilirubin levels at 0 to 4 days of age, the rate of jaundice requiring phototherapy, the neonatal hematological status at 1 to 3 days after birth.
Results: Compared with the early cord clamping group, the neonatal transcutaneous bilirubin level did not differ and the neonatal hematological status (hemoglobin and hematocrit levels) were improved in combined and three subgroups of delayed cord clamping group. Increasing the duration of cord clamping from 90 s to 120 s did not result in further increases in hemoglobin and hematocrit levels but led to a trend towards a higher risk of neonatal jaundice requiring phototherapy and neonatal polycythemia.
Conclusions: Delayed cord clamping for < 90 s in healthy term infants may not only improve the early hematological status of newborns but also avoid excessive neonatal jaundice requiring phototherapy.

1. Introduction

Early cord clamping (ECC) generally occurs immediately or within the first 15 s after birth, which is a part of active management of third stage labor for decades [1]. Delayed cord clamping (DCC) is defined as a delay of at least 30 s between the delivery of the infant and clamping of the umbilical cord [2]. DCC could increase the physiologic placental transfusion, which provides infants approximately a 20 to 30% increase in blood volume and a 50% increase in red cell volume [3,4]. These addition blood theoretically could reduce risk for resuscitation, improve iron stores and thereby improved infants' and children's neurodevelopment, but result in hyperbilirubinemia, polycythemia and jaundice in neonates. A growing body of research demonstrates many clinical benefits of DCC versus ECC, including higher hemoglobin and hematocrit levels [3,5], higher blood pressure [6,7], reduced need for blood transfusion [8], increased total body iron stores [9,10], improved infants' neurodevelopment [11,12] in term or preterm infants, as well as lower rates of intraventricular hemorrhage (IVH) in preterm infants [13,14].

However, DCC has not been adopted widely in obstetricians and midwives as a routine procedure in China [15], which may due to fear of polycythemia, hyperbilirubinemia, jaundice and increased requirement of phototherapy. For term newborns, one study [16] from healthy Japanese newborns found that the rate of jaundice requiring phototherapy could be elevated with DCC, while other studies [3,17,18] showed that no difference in severe hyperbilirubinemia and jaundice requiring phototherapy was observed between ECC group and DCC group.

Furthermore, the duration of DCC was variable, ranging from 30 s to 5 min or to the time of the cord stops pulsating, the optimal cord

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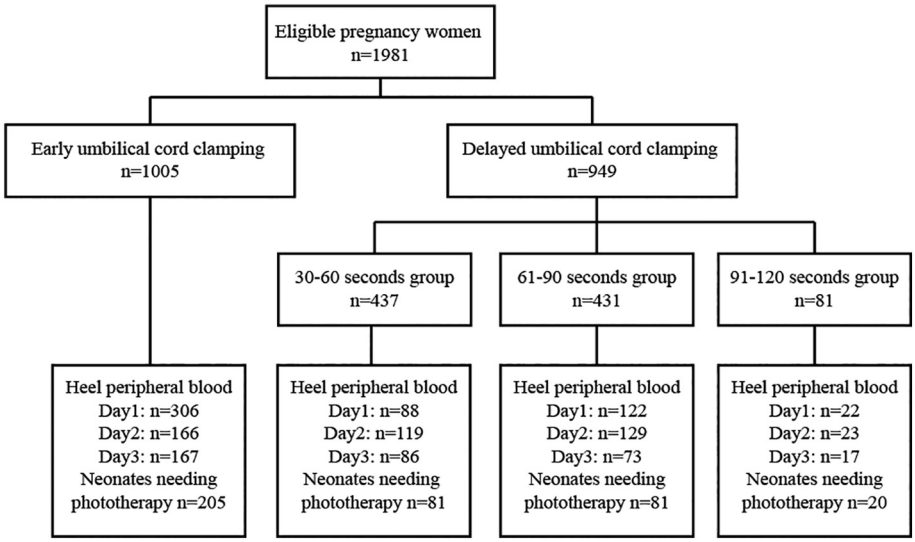

Fig. 1. Flow of study subjects.

Table 1
Baseline characteristics of the study groups.

	ECC group (n = 1005)	DCC group (n = 949)	30–60 s group (n = 437)	61–90 s group (n = 431)	91–120 s group (n = 81)	P^a	P^b
Mother's age (years)	26.27 ± 4.59	26.17 ± 4.38	26.26 ± 4.31	26.01 ± 4.37	26.53 ± 4.58	0.625	0.68
Gravidity	2 (1–3)	2 (1–3)	2 (1–3)	2 (1–3)	2 (1–3)	0.723	0.053
Parity	2 (1–2)	2 (1–2)	2 (1–2)	1 (1–2)	2 (1–2)	0.480	0.042
Gestational age (weeks)	39.63 ± 0.99	39.55 ± 1.02	39.54 ± 1.05	39.53 ± 0.98	39.74 ± 1.03	0.109	0.116
Newborn weight (g)	3320.13 ± 332.88	3313.36 ± 334.53	3296.75 ± 342.83	3316 ± 325.84	3385.66 ± 327.10	0.654	0,141
Fetal sex, Male (%)	522 (51.9)	462 (48.7)	202 (46.2)	215 (49.9)	45 (55.6)	0.15	0.179
Apgar scores at 1 min	10(10 − 10)	10(10–10)	10(10–10)	10(10–10)	10(10–10)	0.394	0.126
Apgar scores at 5 min	10(10–10)	10(10–10)	10(10–10)	10(10–10)	10(10–10)	0.711	0.810

Data are given as mean ± SD, n (%) or median (range).
[a] The comparison between ECC group and DCC group.
[b] The comparison among ECC group and the three subgroups of DCC group.

clamping time remained controversial [2,3,11]. More evidence from clinical trials was needed to determine the best time to clamp the cord. Therefore, in the present study, we conducted a retrospective cohort study in singleton vaginally delivered term neonates to assess the effect of different cord clamping time (< 10 s, 30–60 s, 61–90 s, 91–120 s) on neonatal jaundice.

2. Methods

This was a retrospective cohort study by reviewing electronic medical records of the women with singleton pregnancy who delivered live-born infants vaginally between 37 and 42 weeks gestation at Jiaxing Xiuzhou District Maternal and Child Health Hospital in Province Zhejiang in China from April 1st, 2017 to April 30th, 2018. Exclusion criteria were women with instrumental delivery, Rhesus negative blood group or other blood system disease, clinical disease (diabetes, preeclampsia, hypertension disorders) or any other complications (polyhydramnios, oligohydramnios, placenta praevia, and abruptio placentae), and fetal birth weight < 2.5 kg or > 4.0 kg, newborns with major congenital malformations (congenital anal atresia, congenital biliary atresia, congenital heart disease and so on, whether prenatal suspicion or diagnosis postpartum), or neonatal pneumonia, hemolytic disease and other diseases affecting bilirubin metabolism. Women with incomplete information on umbilical cord management technique during delivery were also excluded. At the time of the initial hospital delivery, the pregnant woman signed an informed consent that she agreed to the instructions of doctors during delivery and her clinical data could be used for scientific research. The study was approved by Jiaxing Xiuzhou District Maternal and Child Health Hospital for Women & Newborns Human Research Protection Office.

The pregnant women were categorized into ECC group, defined as a mother who received umbilical cord clamping before 15 s, or DCC group, defined as a mother who received umbilical cord clamping at least 30 s. Then, DCC group was divided into three subgroups according to a different time (30–60 s, 61–90 s, 91–120 s). The time between the delivery of the infant and clamping of the umbilical cord was clocked by a timer. Baseline characteristics were recorded such as age, gravidity, parity, gestational age, maternal hemoglobin, fetal birth weight, fetal sex and 1 min and 5 min Apgar scores. The primary outcomes were transcutaneous bilirubin levels at 0 to 4 days of age and the number of jaundice requiring phototherapy in newborns. Secondary outcomes included neonatal hematocrit and hemoglobin value on days 1, 2, and 3 of life, the incidence of neonatal anemia and erythrocytosis.

Heel peripheral blood samples from newborns were collected by trained nurses with the standardized procedures for testing the hemoglobin and hematocrit on day 1, 2 and 3 of life. The Transcutaneous bilirubin was measured by the uniform TcB device three times a day (JM-103, KONICA MINOLTA, Japan), and the value of transcutaneous bilirubin is the maximum in the same day. The decision to phototherapy was made clinically at the discretion of the attending neonatologist, in accordance with our unit's recommendations based on the American Academy of Pediatric clinical practice guidelines for phototherapy in hospitalized infants of 35 or more weeks' gestation [19], and serum sample had been measured before the hyperbilirubinemia diagnosed. This phototherapy policy did not change during the study period. The definition of polycythemia is a venous hematocrit value > 65% [20].

Table 2
Neonatal transcutaneous bilirubin levels and the rate of phototherapy.

	ECC group (n = 1005)	DCC group (n = 949)	30–60 s group (n = 437)	61–90 s group (n = 431)	91–120 s group (n = 81)	P^a	P^b
Cord clamping time (s)	10 (9–12)	65(60–80)	60 (50–60)	75 (70–80)	110 (99–120)		
Transcutaneous bilirubin in day 0 of age (μmol/L)	1.70 ± 1.06	1.81 ± 0.88	1.81 ± 0.85	1.81 ± 0.91	1.80 ± 0.88	0.089	F = 0.270, P = .603
Transcutaneous bilirubin in day 1 of age (μmol/L)	5.06 ± 1.94	5.08 ± 1.81	4.98 ± 1.77	5.18 ± 1.85	5.08 ± 1.80	0.818	
Transcutaneous bilirubin in day 2 of age (μmol/L)	9.10 ± 2.03	9.14 ± 2.12	9.02 ± 2.07	9.24 ± 2.16	9.28 ± 2.11	0.696	
Transcutaneous bilirubin in day 3 of age (μmol/L)	11.40 ± 2.26	11.43 ± 2.38	11.39 ± 2.43	11.46 ± 2.34	11.52 ± 2.37	0.743	
Transcutaneous bilirubin in day 4 of age (μmol/L)	12.07 ± 2.16	12.09 ± 2.56	11.93 ± 2.69	12.26 ± 2.36	12.04 ± 2.74	0.902	
Neonates needing phototherapy (%)	205 (20.4)	182 (19.2)	81 (18.5)	81 (18.8)	20 (24.7)	0.499	0.540

Data are given as mean ± SD, n (%) or median (range).
[a] The comparison between ECC group and DCC group.
[b] The comparison among ECC group and the three subgroups of DCC group.

SPSS 19.0 software was used for all statistical analysis. Normally distributed continuous variables were described as means and SD. Student's *t*-test was used for continuous variables with normal distributions between the ECC group and DCC group and one-way ANOVA with the LSD post hoc test was used among the three subgroups of DCC and ECC group except transcutaneous bilirubin levels at different time were analyzed by repetitive measure ANOVA. Pearson's Chi-square tests or Mann-Whitney *U* test was used for categorical variables and data were presented as the total number (%). Maternal blood loss amount was compared among the three subgroups of DCC and ECC group by the Mann-Whitney U test. A p-value < 0.05 was considered statistically significant.

3. Results

As shown in Fig. 1, 1981 eligible pregnant women were enrolled in our study. Their babies were born including 1005 infants with early umbilical cord clamping (51.4%) and 949 with delayed umbilical cord clamping (48.6%). DCC group was divided into three subgroups, 30–60 s group (n = 437 (46.1%)), 61–90 s group (n = 431 (45.4%)) and 91–120 s group (n = 81 (8.5%)). The number of heel peripheral blood samples on the day 1, 2 and 3 of life and neonates needing phototherapy were showed in Fig. 1 respectively.

There was no significant difference in demographic characteristics between the ECC group and DCC group or among the three subgroups of DCC ($P > 0.05$), except the parity among the ECC group and the three subgroups of DCC group ($P < 0.05$) (Table 1). And the time of cord clamping was given in Table 2. The neonatal transcutaneous bilirubin levels in days 0 to 4 of life and neonates needing phototherapy did not differ between the DCC group and ECC group or among three subgroups of DCC ($P > 0.05$) (Table 2). However, the requirement of phototherapy for neonatal jaundice showed a non-significant increase from 20.4% in the ECC group to 24.7% in the 91–120 s group (Table 2).

The hematological status of neonate in the first three days of life after birth was shown in Table 3. Compared with the ECC group, the neonatal hemoglobin and hematocrit levels on the first, second and third days after birth were significantly higher in DCC group, especially in 61–90 s group ($P < 0.05$). Increasing the duration of delayed cord clamping from 90 s to 120 s did not result in further increases in hemoglobin and hematocrit levels. Seven cases of neonatal anemia were diagnosed in the ECC group, and just one case of neonatal anemia was found in the DCC group (results not shown). Compared to ECC group, a higher rate of neonatal polycythemia was detected in the three subgroups of DCC or the combined DCC groups on the first day after birth ($P < 0.05$) but not in the second and third day ($P > 0.05$) (Table 3). Additionally, a statistically significant difference in the rate of neonatal polycythemia was shown among the three subgroups of the DCC group. The rate of neonatal polycythemia in the first day after birth showed a significant increase from 12.4% in the ECC group to 27.3% in the 91–120 s group.

4. Discussion

To our knowledge, this is the first observation that evaluated bilirubin levels within the first 4 days after different durations of cord clamping in term infants by vaginal delivery. Compared with the ECC group, the neonatal transcutaneous bilirubin level in day 0 to 4 of life and neonates needing phototherapy did not differ in three subgroups of DCC or combined DCC group, but there was an increase of about 4% in the requirement of phototherapy for neonatal jaundice in 91–120 s group. The neonatal hemoglobin and hematocrit levels within 3 days after birth were significantly higher in the combined DCC group, with a significant increase only in the 61–90 s group. DCC was associated with less neonatal anemia, a higher rate of polycythemia tested on the first day after birth.

Unlike other studies measured bilirubin levels in term infants at 6 h

Table 3
The hematological status of neonates within 3 days of life.

	ECC group	DCC group	30–60 s group	61–90 s group	91–120 s group	P^a	P^b
Day 1	(n = 306)	(n = 232)	(n = 88)	(n = 122)	(n = 22)		
Neonatal hemoglobin (g/L)	199.35 ± 19.85	204.49 ± 22.26	203.86 ± 23.25	204.80 ± 21.56*	205.27 ± 22.98	0.006	0.046
Neonatal hematocrit (%)	61.97 ± 6.79	63.59 ± 7.63	63.31 ± 7.93	63.69 ± 7.44*	64.12 ± 7.73	0.011	0.074
Neonatal polycythemia (%)	38(12.4)	52(22.4)	22 (25)	24 (19.7)	6 (27.3)	0.002	0.012
Day 2	(n = 166)	(n = 271)	(n = 119)	(n = 129)	(n = 23)		
Neonatal hemoglobin (g/L)	196.90 ± 22.09	204.02 ± 19.55	204.31 ± 19.02	204.22 ± 19.85*	201.43 ± 21.24	0.001	0.006
Neonatal hematocrit (%)	60.76 ± 7.70	63.04 ± 7.01	63.15 ± 6.68	63.14 ± 7.17*	61.89 ± 7.96	0.002	0.014
Neonatal polycythemia (%)	18 (10.8)	44 (16.2)	18 (15.1)	23 (17.8)	3 (13.0)	0.112	0.374
Day 3	(n = 167)	(n = 176)	(n = 86)	(n = 73)	(n = 17)		
Neonatal hemoglobin (g/L)	190.98 ± 22.19	197.04 ± 19.79	195.15 ± 21.03	200.30 ± 19.09*	192.59 ± 14.38	0.008	0.017
Neonatal hematocrit (%)	57.92 ± 7.92	60.20 ± 7.25	59.73 ± 7.72	61.24 ± 6.89*	58.06 ± 5.82	0.006	0.014
Neonatal polycythemia (%)	11(6.6)	17 (9.7)	9 (10.5)	7 (9.6)	1 (5.9)	0.299	0.689

Data are given as mean ± SD or n (%).
[a] The comparison between ECC group and DCC group.
[b] The comparison among ECC group and the three subgroups of DCC group.
* A statistically significant difference comparing with ECC group (one way ANOVA with LSD post hoc test): $P < 0.05$.

[21] or at 24–48 h after birth [3,22], we measured transcutaneous bilirubin levels within 4 days of life in term newborns. No significant difference in bilirubin levels and neonates needing phototherapy was found between DCC and ECC group in our study, which was consistent with the study of term infants born to Libyan mothers [22] and American mothers [3]. Jaleel et al. detected that serum bilirubin after 6 h of birth were slightly higher in the DCC group as compared to the ECC group, but it was not significant [21]. However, in healthy term newborns from Japan, jaundice requiring phototherapy mostly occurred in the DCC group due to the high levels of cord blood hemoglobin [16]. In the present study, we observed that the neonatal hemoglobin and hematocrit levels within 3 days after birth were significantly higher in the DCC group versus the ECC group.

Both previous studies [3,18,22] and ours did not find the higher bilirubin level in the infants with DCC, which may be the result of the bilirubin from the amount of extra blood volume might be too small or too fastly metabolized to make a difference. It is worth noting that the requirement of phototherapy for neonatal jaundice showed an increasing trend in the 91–120 s group. Although DCC did not affect the average level of transcutaneous bilirubin in newborns, it may elevate the peak transcutaneous bilirubin in certain infants and increase the number of neonates needed phototherapy. Therefore, for term healthy newborns with a very low incidence of anemia, DCC for > 90 s may not necessary in view of the higher rate of phototherapy.

The neonatal polycythemia is divided into active polycythemia and passive polycythemia [20]. DCC causes an increase in fetal blood volume resulting from an addition placental transfusion, which is an important factor for passive polycythemia in neonates [20]. In the present study, DCC was associated with a higher rate of neonatal polycythemia in the first day after birth but not in the second and third day, which may be due to the rapid metabolism. The rate of neonatal polycythemia in the first day after birth was the highest in 91–120 s group, which suggested that the incidence of neonatal polycythemia was closely related to the duration of DCC. A prospective observational study [23] reported that DCC was associated with a significant decrease in pH, oxygen saturation, glycemia, oxygen content. So, we speculated that DCC may lead to transient hypoxia, which may be another reason for increased neonatal polycythemia. However, the reason for the similar rates of neonatal polycythemia between the 91–120 s group and the 30–60 s group on the first day was unclear. In the future, more prospective multicenter studies are needed to explore the impact of DCC on the neonatal polycythemia. Increasing the duration of delayed cord clamping > 90 s requires caution due to the high incidence of neonatal polycythemia. However, it was observed that more polycythemia occurred in the DCC group without severe symptomatic polycythemia and obvious adverse outcome, which goes along with other authors' observations [3]. Two major meta-analysis had concluded that DCC in term infants improved the hematological status of the babies in early infancy [1,24] without increases in hyperbilirubinemia or symptomatic polycythemia [24].

DCC was an effective intervention that provided significant benefits of raised hemoglobin and hematocrit levels in term infants [3,21,25]. Likewise, we found that term infants had a early hematological advantage of DCC within 3 days after birth, but no difference in values of hemoglobin or hematocrit was found among the three subgroups of DCC. DCC of at least 30 s after birth could provide an additional 30% blood volume to infants and increase infants' mean blood volume from 62.7 mL/kg to 74.4 mL/kg [18,26]. As described in published study, the majority of the blood transfer from the placenta to the infant occurred in the first minute after delivery [3,27]. A study from Japan reported that Asian babies with DCC of > 60 s, on a racial basis, are more likely to develop jaundice requiring phototherapy, which suggested the duration of DCC should be < 60 s [16]. Therefore, DCC for < 90 s was enough to improve hemodynamic outcomes in term infants with avoiding more neonatal jaundice requiring phototherapy.

There were several limitations to this study. Firstly, our retrospective approach limited the generalizability/power of findings. Secondly, we were unable to obtain blood samples on every infant included in the study, although the plasma bilirubin levels are the golden standard of the degree of bilirubin, as it is an invasion operation for neonates. Moreover, we could not show the clinical significance of DCC on the prevention of anemia because relatively few neonates in either group diagnosed as anemia. The strengths of this study included a large total sample size (n = 1981) and measuring the bilirubin levels in the first 4 days of life. Up till now, there were few studies to assess the bilirubin levels with repeated measurement. Compare with other studies measured the level of bilirubin only once time, repeated measurement could ensure accurate reporting of the effect of the simple intervention on bilirubin levels.

Our study documented that DCC for < 90 s in term infants by vaginal delivery could improve infants' hematological status, although accompanying asymptomatic polycythemia which rapidly resolved. But increasing the duration of DCC from 90 s to 120 s did not observe further increases in hemoglobin and hematocrit levels but with a trend towards higher risk of neonatal jaundice requiring phototherapy and neonatal polycythemia. Therefore, we concluded that 90 s of DCC may not only improve the early hematology outcomes of the newborn but also avoid excessive incidence rate of neonatal jaundice requiring phototherapy and neonatal polycythemia. Further studies are needed to improve the power of findings by design the RCT and to report the impact of the different timing of cord clamping on the more neonatal outcomes including neonatal bilirubin encephalopathy, anemia and the

number of neonates needing blood transfusion.

Author statement

All authors have materially participated in the research and/or article preparation. Yiyu Qian and Qiujing Lu analyzed data, prepared the initial draft, and critically reviewed the manuscript. Hailing Shao check and rectify the statistical methods uesd and checked the expressions and spellings errors of the whole article. Xinxin Ying and Wenle Huang participated in data collection, organization, analysis. Ying Hua design, interpretation, reviewed the manuscript and approved submission.

We have seen and approved the final version and that it has neither been published nor submitted elsewhere. We also declare that I have no conflict of interest, other than any noted in the covering letter to the editor.

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Declaration of competing interest

Neither of the authors have any conflicts of interest to declare.

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